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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09   CA/CAplus records now contain indexing from 1907 to the
                   present
 NEWS  4  DEC 08   INPADOC: Legal Status data reloaded
 NEWS  5  SEP 29   DISSABS now available on STN
 NEWS  6  OCT 10   PCTFULL: Two new display fields added
 NEWS  7  OCT 21   BIOSIS file reloaded and enhanced
 NEWS  8  OCT 28   BIOSIS file segment of TOXCENTER reloaded and enhanced
 NEWS  9  NOV 24   MSDS-CCOHS file reloaded
 NEWS 10  DEC 08   CABA reloaded with left truncation
 NEWS 11  DEC 08   IMS file names changed
 NEWS 12  DEC 09   Experimental property data collected by CAS now available
                   in REGISTRY
 NEWS 13  DEC 09   STN Entry Date available for display in REGISTRY and CA/CAplus
 NEWS 14  DEC 17   DGENE: Two new display fields added
 NEWS 15  DEC 18   BIOTECHNO no longer updated
 NEWS 16  DEC 19   CROPU no longer updated; subscriber discount no longer
                   available
 NEWS 17  DEC 22   Additional INPI reactions and pre-1907 documents added to CAS
                   databases
 NEWS 18  DEC 22   IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
 NEWS 19  DEC 22   ABI-INFORM now available on STN
 NEWS 20  JAN 27   Source of Registration (SR) information in REGISTRY updated
                   and searchable
 NEWS 21  JAN 27   A new search aid, the Company Name Thesaurus, available in
                   CA/CAplus
 NEWS 22  FEB 05   German (DE) application and patent publication number format
                   changes
 NEWS 23  MAR 03   MEDLINE and LMEDLINE reloaded
 NEWS 24  MAR 03   MEDLINE file segment of TOXCENTER reloaded
 NEWS 25  MAR 03   FRANCEPAT now available on STN

 NEWS EXPRESS  DECEMBER 28 CURRENT WINDOWS VERSION IS V7.00, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003
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FILE 'HOME' ENTERED AT 13:55:02 ON 04 MAR 2004

=> file uspatful
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.42       0.42

FILE 'USPATFULL' ENTERED AT 13:56:10 ON 04 MAR 2004
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 4 Mar 2004 (20040304/PD)
FILE LAST UPDATED: 4 Mar 2004 (20040304/ED)
HIGHEST GRANTED PATENT NUMBER: US6701528
HIGHEST APPLICATION PUBLICATION NUMBER: US2004045070
CA INDEXING IS CURRENT THROUGH 4 Mar 2004 (20040304/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 4 Mar 2004 (20040304/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2003

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

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=> e saxinger carl/in
E1          12     SAXHOLM ROLF/IN
E2           3     SAXINGER ALLAN L/IN
E3           3 --> SAXINGER CARL/IN
E4           3     SAXINGER CARL W/IN
E5           1     SAXINGER W CARL/IN
E6           4     SAXL ERWIN J/IN
E7           6     SAXL KAREL/IN
E8           3     SAXLER ADAM WILLIAM/IN
E9           2     SAXLER WOLFGANG/IN
E10          2     SAXLUND ODDMUND/IN
E11          1     SAXLUND PENTTI/IN
E12          2     SAXLUND RAIMO/IN

=> s e3 or e4
             3 "SAXINGER CARL"/IN
             3 "SAXINGER CARL W"/IN
L1           6 "SAXINGER CARL"/IN OR "SAXINGER CARL W"/IN

=> d l1,ti,1-6

L1   ANSWER 1 OF 6  USPATFULL on STN
TI     Polypeptides comprising IL-6 ligand-binding receptor domains

L1   ANSWER 2 OF 6  USPATFULL on STN
TI     Polypeptides that bind HIV gp120 and related nucleic acids, antibodies,
       compositions, and methods of use

L1   ANSWER 3 OF 6  USPATFULL on STN
TI     Antibodies against human herpesvirus-6(HHV-6) and method of use

L1   ANSWER 4 OF 6  USPATFULL on STN
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Automated peptide design and synthesis

L1 ANSWER 5 OF 6 USPATFULL on STN
TI Human herpesvirus-6 (HHV-6) isolation and products

L1 ANSWER 6 OF 6 USPATFULL on STN
TI Human herpesvirus-6(HHV-6)Isolution and Products

=> d l2,cbib,ab,clm,2
L2 NOT FOUND
The L-number entered has not been defined in this session, or it has been deleted. To see the L-numbers currently defined in this session, enter DISPLAY HISTORY at an arrow prompt (=>).

=> d l1,cbib,ab,clm,2

L1 ANSWER 2 OF 6 USPATFULL on STN
2003:99510 Polypeptides that bind HIV gp120 and related nucleic acids, antibodies, compositions, and methods of use.
Saxinger, Carl, Bethesda, MD, UNITED STATES
Department of Health and Human Services, Rockville, MD (U.S. corporation)
US 2003068615 A1 20030410
APPLICATION: US 2002-84813 A1 20020227 (10)
PRIORITY: US 1999-151270P 19990827 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides, among other things, a polypeptide that binds with the gp120 envelope protein of HIV, in particular HIV-1, under physiological conditions, a nucleic acid that encodes such a polypeptide and can be expressed in a cell, a composition comprising such a polypeptide or nucleic acid or an antibody and a carrier therefor, a composition comprising a solid support matrix to which is attached an above-described polypeptide or an anti-antibody to a specified polypeptide sequence, a method of making an antibody to gp120, and a method of removing HIV from a bodily fluid.

CLM What is claimed is:

1. A polypeptide comprising the amino acid sequence YDIXYYXXE, wherein X is any synthetic or naturally occurring amino acid residue, such that the polypeptide binds HIV gp120 under physiological conditions, and wherein said polypeptide comprises less than about 100 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human CCR5 chemokine receptor.

2. The polypeptide of claim 1, which comprises less than about 50 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human CCR5 chemokine receptor.

3. The polypeptide of claim 2, which comprises less than about 25 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human CCR5 chemokine receptor.

4. The polypeptide of claim 3, which comprises less than about 13 amino acids that are identical to or substantially identical to the amino acid sequence of the human CCR5 chemokine receptor.

5. The polypeptide of claim 4, which consists essentially of YDIXYYXXE.

6. The polypeptide of any of claims 1-5, which comprises the amino acid sequence YDIN*YYT*S*E, wherein N* is asparaginyl or a synthetic or naturally occurring substitute therefor, T* is threoninyl or a synthetic or naturally occurring substitute therefor, and S* is serinyl or a synthetic or naturally occurring substitute therefor.

7. The polypeptide of claim 6, wherein N* is asparaginyl, T* is threoninyl, and S* is serinyl.

8. The polypeptide of any of claims 1-6, comprising the amino acid sequence M*D*YQ*V*S*SP*IYDIN*YYT*S*E, wherein each letter indicates the standard amino acid residue designated by that letter, and a letter followed directly by an * indicates that any synthetic or naturally occurring amino acid can occupy that position.

9. The polypeptide of claim 8, wherein said letter followed directly by an * indicates the amino acid residue represented by the letter or a synthetic or naturally occurring conservative or neutral amino acid substitution therefor.

10. The polypeptide of claim 9, wherein said amino acid sequence is MDYQVSSPIYDINYYTSE.

11. A polypeptide comprising the amino acid sequence XEXIXIYXXXNYXXX, wherein X is any synthetic or naturally occurring amino acid, such that the polypeptide binds HIV gp120 under physiological conditions, and wherein said polypeptide less than about 100 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human CXCR4 chemokine receptor.

12. The polypeptide of claim 11, which comprises less than about 50 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human CXCR4 chemokine receptor.

13. The polypeptide of claim 11, which comprises less than 25 contigous amino acids that are identical to or substantially identical to the amino acid sequence of the human CXCR4 chemokine receptor.

14. The polypeptide of claim 13, which consists essentially of EXIXIYXXXNY.

15. The polypeptide of any of claims 11-14, which comprises the amino acid sequence M*EG*IS*IYT*S*D*NYT*E*E*, wherein each letter indicates the standard amino acid residue designated by that letter, and each letter followed directly by an * indicates the amino acid residue represented by the letter or a synthetic or naturally occurring conservative or neutral amino acid substitution therefor.

16. The polypeptide of claim 15, wherein said amino acid sequence M*EG*IS*IYT*S*D*NYT*E*E* is M*EGISIYTSDNYT*E*E*.

17. A polypeptide comprising the amino acid sequence EHQAFLQFS, such that the polypeptide binds with HIV gp120 under physiological conditions and wherein said polypeptide comprises less than about 100 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human STRL33 chemokine receptor.

18. The polypeptide of claim 17, which comprises less than about 50 contiguous amino acid that are identical to or substantially identical to the amino acid sequence of the human STRL33 chemokine receptor.

19. The polypeptide of claim 18, which comprises less than about 25 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human STRL33 chemokine receptor.

20. The polypeptide of claim 19, which consists essentially of the sequence EHQAFLQFS.

21. A polypeptide comprising at least a portion or all of an amino acid sequence selected from the group consisting of LPPLYSLVFIFGFVGNML, QWDFGNTMCQLLTGLYFIGFFS, SQYQFWKNFQTLKIVILG, APYNIVLLLNTFQEFFGLNNCS, and YAFVGEKFRNYLLVFFQK, wherein the polypeptide binds with HIV gp120 under physiological conditions and comprises less than about 100 amino acid residues that are identical to or substantially identical to the amino

acid sequence of the human CCR5 chemokine receptor.

22. A polypeptide comprising at least a portion or all of an amino acid sequence selected from the group consisting of LLLTIPDFIFANVSEADD (165-182), VVFQFQHIMVGLILPGIV (197-214), and IDSFILLEIIKQGCEFEN (261-278), wherein the polypeptide binds with HIV gp120 under physiological conditions and comprises less than about 100 amino acid residues that are identical to or substantially identical to the amino acid sequence of the human CXCR4 chemokine receptor.

23. A polypeptide comprising at least a portion or all of an amino acid sequence selected from the group consisting of LVISIFYHKLQSLTDVFL (53-70), PFWAYAGIHEWVFGQVMC (85-102), EAISTVVLATQMTLGFFL (185-202), LTMIVCYSVIIKTLLHAG (205-222), MAVFLLTQMPFNLMKFIRSTHW (237-258), HWEYYAMTSFHYTIMVTE (257-274), ACLNPVLYAFVSLKFRKN (281-298) and SKTFSASHNVEATSMFQL (325-342), wherein the polypeptide binds with-HIV gp120 under physiological conditions and comprises less than about 100 amino acid residues that are identical to or substantially identical to the amino acid sequence of the human STRL33 chemokine receptor.

24. A polypeptide comprising at least a portion of or all of an amino acid sequence selected from the group consisting of DTYICEVED, EEVQLLVFGLTANSD, THLLQGQSLTLTLES, and GEQVEFSFPLAFTVE, wherein the polypeptide binds with HIV gp120 under physiological conditions and wherein the polypeptide comprises less than about 100 amino acids that are identical to or substantially identical to the amino acid sequence of the human CD4 cell-surface protein.

25. A polypeptide of any of claims 21-24, which comprises all of the amino acid sequence and 0 to about 6 conservative or neutral amino acid substitutions.

26. The polypeptide of claim 25, comprising 0 amino acid substitutions.

27. The polypeptide of any of claims 21-26, which comprises less than about 50 amino acids that are identical to or substantially identical to a protein that naturally has the amino acid sequence.

28. The polypeptide of any of claims 21-26, which comprises less than about 25 amino acids that are identical to or substantially identical to a protein that naturally has the amino acid sequence.

29. The polypeptide of any of claims 1-28, wherein said polypeptide further comprises a pharmaceutically acceptable substituent.

30. A composition comprising the polypeptide of any of claims 1-28, and a carrier.

31. A nucleic acid encoding the polypeptide of any of claims 1-28, wherein said nucleic acid can be expressed in a cell.

32. The nucleic acid of claim 31, further comprising a nucleic acid sequence that encodes a signal sequence, wherein said signal sequence is translated as a fusion protein with the polypeptide to form a signal sequence-polypeptide fusion, and wherein said signal sequence can cause secretion of at least the polypeptide out of a cell in which the nucleic acid is expressed.

33. A vector comprising the nucleic acid of claim 31 or 32.

34. A method of making an antibody, which method comprises administering an immunogenic amount of a polypeptide of any of claims 1-28 or a nucleic acid of any of claims 31 or 33 to an animal.

35. A method of prophylactically or therapeutically treating HIV infection in a mammal in need thereof, which method comprises

administering to said mammal an effective amount of a polypeptide of any of claims 1-28, a nucleic acid of any of claims 31-33, or an anti-antibody to a polypeptide of any of claims 1-28.

36. A method of making an antibody that binds to a gp120 envelope protein of a human immunodeficiency virus-1 (HIV-1), said method comprising: (a) labeling a polypeptide of any of claims 1-28 to obtain a labeled compound, (b) providing a library of synthetic peptides, wherein said library consists of a multiplicity of synthetically-produced polypeptides that are homologous to a continuous region of an HIV-1 gp120 envelope protein, wherein each polypeptide of said library is substantially isolated from every other polypeptide of said library and is located in a known position, (c) individually contacting each polypeptide with said labeled compound such that a portion of the labeled compound can bind with the polypeptide, thereby producing a bound population of each polypeptide and an unbound population of each polypeptide, (d) removing substantially all of the unbound labeled compound from the position occupied by each polypeptide, (e) measuring the amount of labeled compound that remains co-localized with each polypeptide, to determine the quantity of labeled compound bound by each polypeptide, (f) evaluating the amount of labeled compound bound by each polypeptide to identify a portion of the HIV-1 gp120 envelope protein that binds to an (HIV-1)-receptor selected from the group consisting of CCR5, CXCR4, STRL33, and CD4, (g) providing an immunizing compound comprising a polypeptide comprising an amino acid sequence that is homologous to said portion of the HIV-1 gp120 envelope protein, (h) inserting an immunogenic quantity of said immunizing compound into an animal to cause said animal to produce an antibody that binds with said portion of the HIV-1 gp120 envelope protein.

37. The method of claim 36, wherein said labeled compound comprises a moiety selected from the group consisting of a radioactive atom, an enzyme, a polyhistidinyl moiety, and an antigen that is specifically recognized by a standard antibody.

38. The method of claim 36 or 37, wherein said library consists of a multiplicity of synthetically-produced polypeptides that are identical to a continuous region of an HIV-1 gp120 envelope protein.

39. The method of any of claims 36-38, wherein said polypeptides contain at least about 6 amino acid residues and no more than about 45 amino acid residues.

40. The method of claim 39, wherein said polypeptides contain no more than about 30 amino acid residues.

41. The method of any of claims 36-40, wherein said library comprises a multiplicity of polypeptides of identical lengths.

42. The method of any of claims 36-41, wherein said library comprises a multiplicity of polypeptides that are homologous to a region of the HIV-1 gp120 envelope protein and have an offset of n amino acid residues, wherein n is an integer of at least 1 and is not greater than the product of length of the longest polypeptide measured in amino acid residues and 1.5.

43. The method of claim 42, wherein said offset is not greater than the product of length of the longest polypeptide measured in amino acid residues and 1.0.

44. The method of claim 42, wherein said offset is not greater than the product of length of the longest polypeptide measured in amino acid residues and 0.5.

45. The method of claim 42, wherein said offset is not greater than 30.

46. The method of claim 42, wherein said offset is not greater than 15.

47. The method of claim 42, wherein said offset is not greater than 4.

48. The method of any of claims 36-47, wherein each polypeptide is bound to a solid support and is located in a vessel that enables each polypeptide to be covered in a liquid that does not contact any other oligonucleotide of the library.

49. The method of claim 48, wherein each polypeptide is bound to a bead in a vessel or is bound to the well of a multi-well assay plate.

50. The method of claim 36, wherein said step of removing substantially all of the unbound labeled compound comprises the additional steps of (i) removing a liquid containing said unbound labeled compound from a solid substrate to which an polypeptide of the library is bound, (ii) applying a quantity of wash-liquid to said solid substrate that is sufficient to cover any portion of said solid substrate or a vessel containing said solid substrate that has been contacted by said labeled compound, and (iii) removing said wash-liquid.

51. The method of any of claims 36-50, wherein said immunizing compound comprises an adjuvant or wherein said polypeptide comprising an amino acid sequence that is homologous to said portion of the HIV gp120 envelope protein is conjugated to a known immunogen.

52. The method of any of claims 36-51, wherein said method is performed in a mammal belonging to a group selected from the group consisting of rodents, canines, felines, and ruminants.

53. The immunizing compound of step (g) of the method of any of claims 36-52.

54. An antibody produced by the method of any of claims 36-53.

55. A method of removing HIV from a bodily fluid of a mammal, which method comprises extra-corporeally contacting said bodily fluid with a solid support to which is attached a polypeptide of any of claims 1-28 or an anti-antibody to a polypeptide of any of claims 1-78, or the antibody of claim 54.

=> file wpids

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	5.46	5.88

FILE 'WPIDS' ENTERED AT 13:57:03 ON 04 MAR 2004
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FILE LAST UPDATED: 2 MAR 2004 <20040302/UP>
MOST RECENT DERWENT UPDATE: 200415 <200415/DW>
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=> e saxinger c/in
E1            2     SAXINGER A/IN
E2            3     SAXINGER A L/IN
E3            4 --> SAXINGER C/IN
E4            4     SAXINGER C W/IN
E5            2     SAXINGER W C/IN
E6            1     SAXL D/IN
E7            3     SAXL K/IN
E8            2     SAXLER A W/IN
E9            2     SAXLER W/IN
E10           4     SAXLUND O/IN
E11           1     SAXLUND P/IN
E12           1     SAXLUND R/IN

=> s e3 or e4
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              4 "SAXINGER C W"/IN
L2            8 "SAXINGER C"/IN OR "SAXINGER C W"/IN

=> d l2,ti,1-8

L2   ANSWER 1 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Novel polypeptides useful for treating HIV infection, have homology to
     regions of domains of human chemokine receptors CCR5, CXCR4 and STRL33,
     and binds to HIV gp120 under physiological conditions.

L2   ANSWER 2 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Polypeptides which inhibit the binding of interleukin (IL)-6 ligand with
     the IL-6 receptor, and the nucleic acids that encode them, useful for
     treating e.g. inflammation and autoimmune diseases.

L2   ANSWER 3 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Isolated human herpes virus HHV-6 - and nucleic acid which hybridises with
     nucleic acid from HHV-6 but not with that of Epstein-Barr virus etc., used
     for detecting HHV-6.

L2   ANSWER 4 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Automated peptide synthesis - using novel solvent resistant substrates and
     novel solns. for storing protected carboxyl terminal aminoacid(s).

L2   ANSWER 5 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Diagnosis of human B-lymphotropic virus infection - spectrophotometrically
     using a pure, soluble, viral antigen lysate, test serum and labelled
     antibodies.

L2   ANSWER 6 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   New mol. clone of Human B Lymphotropic Virus - and diagnosis of virus in
     vitro in samples of infected blood serum.

L2   ANSWER 7 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Human B Lymphotropic virus - used in detecting haematopoietic malignancy
     including B-cell lymphoma of both AIDS and non-AIDS origin.

L2   ANSWER 8 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Assay for human T-cell leukaemia virus type III - useful for detecting
     AIDS.
```

-> d 12,bib,ab,clm,1
'CLM' IS NOT A VALID FORMAT FOR FILE 'WPIDS'

The following are valid formats:

TRI	SAM	Short Information (Syn.: TRIAL,SAMPLE)
STR		DERWENT Chemical Resource Structure
BIB		Bibliographic Data
BRIEFG.H		Brief Contents of Document with GI.H
BRIEFG		Brief Contents of Document with GI
BRIEF		Brief Contents of Document
IBRIEFG.H		Brief Contents of Document with GI.H, Indented Version
IBRIEFG		Brief Contents of Document with GI, Indented Version
IBRIEF		Brief Contents of Document, Indented Version
MAXG		All Data with GIS and GI.H
MAX		All Data
ALLG.H		All Data Except ABEQ, CMC, and PLC with GI.H
ALLG		All Data Except ABEQ, CMC, and PLC with GI
ALL		All Data Except ABEQ, CMC, and PLC
FULL		All Data Except ABEQ, CMC, and PLC plus TECH and PRIO
FULLG		All Data Except ABEQ, CMC, and PLC with GI plus TECH and PRIO
DALL		Delimited ALL Format
BASIC		Basic Patent Information
STD		Default
IDE		Structure File Default
IALLG.H		Indented Version of ALL Format with GI.H
IALLG		Indented Version of ALL Format with GI
IALL		Indented Version of ALL Format
IFULL		Indented Version of FULL Format
IFULLG		Indented Version of FULLG Format
ISTD		Indented Version of STD Format
IBIB		Indented Version of BIB Format
ABS		All Abstracts
CODE	IND	Manual-, Plasdoc-, and Chemical Code plus Keywords
SUM		Title and Novelty

AB		Abstract (Basic)
ABEQ		Abstract, Equivalent
ADT		Application Details
ADT.B		Application Details Basic
AI	AP	Application Information
AI.B		Application Information Basic
AN		Accession Number
AN.S		DERWENT Chemistry Resource Accession Number, DCR Segment
APPS		Application Number Group
AW		Additional Words
CC		Classification Code (Substance Descriptor
CMC		Chemical Code
CMT		Comment
CN		Chemical Name
CN.P		Chemical Name Preferred
CN.S		Systematic Chemical Name
CR	XR	Cross Reference
CYC		Country Count
DAN		DERWENT Accession Number List
DC		DERWENT Class
DCN		DERWENT Compound Number
DCR		DERWENT Chemistry Resource Accession Number
DCRE		DERWENT Chemistry Resource Number
DCSE		DERWENT Chemistry Resource Number, DCR Segment
DN		Document Number CPI and Non CPI
DNC		Document Number CPI
DNN		Document Number Non CPI
DRN		DERWENT Registry Number
DS		Designated States

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ED             Entry Date
EDCR           Entry Date DERWENT Chemistry Resource
FA             Field Availability
FAS            Field Availability Supplementary Data
FAM            Patent Family
FDT            Filing Details
FG     AM      Fragment Code
FS             File Segment
IC             International Patent Classification
GI             Graphical Information
GI.H           Graphical Information, High Resolution
GIS            Graphical Information Size
ICA            IPC, Additional (Supplementary)
ICI            IPC, Index (Complementary)
ICM            IPC, Main
ICS            IPC, Secondary
IN     AU      Inventor
IPC            International Patent Classification
ISMI           ISOSMILES String
KS             Plasdoc Key Serials
KW             Keyword Indexing, Including DERWENT Chemistry Resource Numbers, DWPI Segment
M0             Chemical Code (Pre 1970)
M1-6           Chemical Codes
MC             Manual Code
MF             Molecular Formula
MW             Molecular Weight
NOV            Novelty
PA     CS      Patent Assignee
PATS           Patent Number Group
PI     PN      Patent Information
PI.B   PN.B    Patent Information Basic
PIA            Patent Information Abbreviated
PIA.B          Patent Information Abbreviated Basic
PLC            Plasdoc Codes
PLE            Enhanced Plasdoc Codes
PNC            Patent Number Count
PRAI   PRN     Priority Information
PRIO           Prior Art
REP    RPN RE  Reference Patent Information
RIN            Ring Index Number
SDCN           Structure Segment DERWENT Compound Number
SDRN           Structure Segment DERWENT Registry Number
SMF            Standardized Molecular Formula
SMIL           SMILES String
SRIN           Structure Segment Ring Index Number
SY             Synonym Name
TECH           Technology Focus
TI             Title
TT             Title Terms
UP             Update Date
UPA            Update Date Plasdoc Code
UPAB           Update Date Abstract
UPB            Update Date Chemical Code
UPCR           Update Date DERWENT Chemistry Resource
UPKW           Update Date Keyword Indexing
UPP            Update Date Patent
UPS            Update Date SDI
UPTX           Update New Content Abstract Fields
UPWX           Update Date WPI Cross Reference
ENTER DISPLAY FORMAT (STD):bib,ab

L2   ANSWER 1 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN   2001-244398 [25]   WPIDS
DNN  N2001-173971       DNC C2001-073337
TI   Novel polypeptides useful for treating HIV infection, have homology to
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regions of domains of human chemokine receptors CCR5, CXCR4 and STRL33, and binds to HIV gp120 under physiological conditions.

DC B04 D16 S03

IN **SAXINGER, C**

PA (USSH) US DEPT HEALTH & HUMAN SERVICES

CYC 94

PI WO 2001016182 A2 20010308 (200125)* EN 114p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000069410 A 20010326 (200137)
US 2003068615 A1 20030410 (200327)

ADT WO 2001016182 A2 WO 2000-US23505 20000825; AU 2000069410 A AU 2000-69410 20000825; US 2003068615 A1 Provisional US 1999-151270P 19990827, Cont of WO 2000-US23505 20000825, US 2002-84813 20020227

FDT AU 2000069410 A Based on WO 2001016182

PRAI US 1999-151270P 19990827; US 2002-84813 20020227

AB WO 200116182 A UPAB: 20010508

NOVELTY - Polypeptides (I) comprising less than about 100 contiguous amino acids that are identical to or substantially identical to regions of domains of human chemokine receptors CCR5, CXCR4 and STRL33, as well as domains of CD4 that bind with human immunodeficiency virus (HIV), in particular to HIV gp120 envelope protein under physiological conditions, are new.

DETAILED DESCRIPTION - (I) comprises:

(a) a sequence (S1) YDIXYYXXE, where X is any synthetic or naturally occurring amino acid residue, identical to or substantially identical to a sequence of human CCR5 chemokine receptor;

(b) a sequence (S2) XEXIXIYXXXNYXXX, where X is any synthetic or naturally occurring amino acid residue, identical to or substantially identical to a sequence of human CXCR4 chemokine receptor;

(c) a sequence (S3) EHQAFLQFS identical to or substantially identical to a sequence of human STRL33 chemokine receptor;

(d) a sequence (S4) comprising at least a portion of sequence LPPLYSLVFIFGFVGNML, QWDFGNTMCQLLTGLYFIGFFS, SQYQFWKNFQTLKIVILG, APYNIVLLLNPFQEFFGLNNCS or YAFVGEKFRNYLLVFFQK, identical to or substantially identical to a sequence of human CCR5 chemokine receptor;

(e) a sequence (S5) comprising at least a portion of sequence LLLTIPDFIFANVSEADD, VVFQFQHIMVGLILPGIV or IDSFILLEIIKQGCEFEN, identical to or substantially identical to a sequence of human CXCR4 chemokine receptor;

(f) a sequence (S6) comprising at least a portion of sequence LVISIFYHKLQSLTDVFL, PFWAYAGIHEWVFGQVMC, EAISTVVLATQMTLGFFL, LTMIVCYSVIIKTLLHAG, MAVFLLTQMPFNLMKFIRSTHW, HWEYYAMTSFHYTIMVTE, ACLNPVLYAFVSLKFRKN or SKTFSASHNVEATSMFQL, identical to or substantially identical to a sequence of human STRL33 chemokine receptor; or

(g) a sequence (S7) comprising at least a portion of sequence DTYICEVED, EEVQLLVFGLTANSD, THLLQGQSLTLTLES or GEQVEFSFPLAFTVE, identical to or substantially identical to a sequence of human CD4 cell surface protein.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition (II) comprising (I);

(2) a nucleic acid (III) encoding (I), which can be expressed in a cell;

(3) a vector (IV) containing (III);

(4) making an antibody that binds to HIV-1 gp120 envelope protein, by labeling (I) to obtain a labeled compound, providing a library of synthetic peptides consisting of a number of synthetically-produced polypeptides that are homologous to a continuous region of a HIV-1 gp120 envelope protein, where each polypeptide of the library is substantially isolated from every other polypeptide of the library and is located in a known position, individually contacting each polypeptide with the labeled compound such that a portion of the labeled compound can bind with the

polypeptide, thereby producing a bound population of each polypeptide and an unbound population of each polypeptide, removing substantially all of the unbound labeled compound from the position occupied by each polypeptide, measuring the amount of labeled compound that remains co-localized with each polypeptide to determine the quantity of labeled compound bound by each polypeptide, evaluating the amount of labeled compound bound by each polypeptide to identify a portion of the HIV-1 gp120 envelope protein that binds to HIV-1 receptor CCR5, CXCR4,STRL33 or CD4, providing an immunizing compound comprising a polypeptide having an amino acid sequence that is analogous to a portion of HIV-1 gp120 envelope protein, and inserting an immunizing compound into an animal to cause the animal to produce an antibody that binds with the portion of HIV-1 gp120 envelope protein; and

(5) an antibody (Ab) produced by the above method.

ACTIVITY - Anti-HIV.

MECHANISM OF ACTION - Vaccine. No supporting data given.

USE - (I) and (III) are useful for making an antibody in an animal. (I) and Ab are useful for removing HIV from a bodily fluid of a mammal, by contacting the bodily fluid with a solid support attached to (I) or Ab, extra-corporeally. (I), (III) and Ab are useful for prophylactically or therapeutically treating HIV infection (claimed).

Dwg.0/1

=> d his

(FILE 'HOME' ENTERED AT 13:55:02 ON 04 MAR 2004)

FILE 'USPATFULL' ENTERED AT 13:56:10 ON 04 MAR 2004
E SAXINGER CARL/IN
L1 6 S E3 OR E4

FILE 'WPIDS' ENTERED AT 13:57:03 ON 04 MAR 2004
E SAXINGER C/IN
L2 8 S E3 OR E4

=> file medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	10.95	16.83

FILE 'MEDLINE' ENTERED AT 13:58:11 ON 04 MAR 2004

FILE LAST UPDATED: 3 MAR 2004 (20040303/UP). FILE COVERS 1953 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> e saxinger c/au

E1	1	SAXILD NICOLAJ/AU
E2	1	SAXIN MARIA/AU
E3	66 -->	SAXINGER C/AU
E4	5	SAXINGER C W/AU
E5	1	SAXINGER W/AU
E6	47	SAXINGER W C/AU
E7	1	SAXIONI E/AU
E8	2	SAXKJAER L/AU
E9	14	SAXL A/AU

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E10           8      SAXL H/AU
E11           5      SAXL J/AU
E12          57      SAXL O/AU

=> s e3 or e4
            66 "SAXINGER C"/AU
             5 "SAXINGER C W"/AU
L3          71 "SAXINGER C"/AU OR "SAXINGER C W"/AU

=> s l3 and (CCR5 or chemokine receptor?)
          2576 CCR5
          9338 CHEMOKINE
        634468 RECEPTOR?
          3695 CHEMOKINE RECEPTOR?
                 (CHEMOKINE(W)RECEPTOR?)
L4           0 L3 AND (CCR5 OR CHEMOKINE RECEPTOR?)

=> s l3 and (HIV or human immunodeficiency virus)
        134297 HIV
       8426654 HUMAN
        112025 IMMUNODEFICIENCY
        369167 VIRUS
         42252 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L5          28 L3 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l5 and (gp120 or gp160)
          5760 GP120
          1415 GP160
L6           2 L5 AND (GP120 OR GP160)

=> d l6,ti,1-2

L6   ANSWER 1 OF 2     MEDLINE on STN
TI   Localization of B-cell stimulatory activity of HIV-1 to the carboxyl
     terminus of gp41.

L6   ANSWER 2 OF 2     MEDLINE on STN
TI   Stages in the progression of HIV infection in chimpanzees.


=> d his

     (FILE 'HOME' ENTERED AT 13:55:02 ON 04 MAR 2004)

     FILE 'USPATFULL' ENTERED AT 13:56:10 ON 04 MAR 2004
                E SAXINGER CARL/IN
L1            6 S E3 OR E4

     FILE 'WPIDS' ENTERED AT 13:57:03 ON 04 MAR 2004
                E SAXINGER C/IN
L2            8 S E3 OR E4

     FILE 'MEDLINE' ENTERED AT 13:58:11 ON 04 MAR 2004
                E SAXINGER C/AU
L3           71 S E3 OR E4
L4            0 S L3 AND (CCR5 OR CHEMOKINE RECEPTOR?)
L5           28 S L3 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L6            2 S L5 AND (GP120 OR GP160)

=> d 15,ti,1-28

L5   ANSWER 1 OF 28     MEDLINE on STN
TI   Mixed-backbone oligonucleotides as second generation antisense
     oligonucleotides: in vitro and in vivo studies.
```

L5 ANSWER 2 OF 28 MEDLINE on STN
TI Nef protein of **HIV**-1 has B-cell stimulatory activity.

L5 ANSWER 3 OF 28 MEDLINE on STN
TI Autopsy findings in **HIV**-infected inner-city patients.

L5 ANSWER 4 OF 28 MEDLINE on STN
TI Sequential measurement of beta 2-microglobulin levels, p24 antigen levels, and antibody titers following transplantation of a **human immunodeficiency virus**-infected kidney allograft.

L5 ANSWER 5 OF 28 MEDLINE on STN
TI Prevalence of antibodies to **human immunodeficiency virus** and to human T cell leukemia virus type I in transfused sickle cell disease patients.

L5 ANSWER 6 OF 28 MEDLINE on STN
TI Examination of HTLV-I ELISA-positive leukemia/lymphoma patients by western blotting gave mostly negative or indeterminate reaction.

L5 ANSWER 7 OF 28 MEDLINE on STN
TI The spectrum of clinical and laboratory findings resulting from human herpesvirus-6 (HHV-6) in patients with mononucleosis-like illnesses not resulting from Epstein-Barr virus or cytomegalovirus.

L5 ANSWER 8 OF 28 MEDLINE on STN
TI Localization of B-cell stimulatory activity of **HIV**-1 to the carboxyl terminus of gp41.

L5 ANSWER 9 OF 28 MEDLINE on STN
TI Influences of related retroviruses on lymphocyte functions.

L5 ANSWER 10 OF 28 MEDLINE on STN
TI No evidence for true HTLV-I or **HIV**-1 antibodies in Finnish Lapps.

L5 ANSWER 11 OF 28 MEDLINE on STN
TI Serologic and immunologic correlates of retroviral infection in transplant recipients.

L5 ANSWER 12 OF 28 MEDLINE on STN
TI Antibody reactivity with HBLV (HHV-6) in U.S. populations.

L5 ANSWER 13 OF 28 MEDLINE on STN
TI Stages in the progression of **HIV** infection in chimpanzees.

L5 ANSWER 14 OF 28 MEDLINE on STN
TI Pathogenetic role of **HIV** infection in Kaposi's sarcoma of equatorial East Africa.

L5 ANSWER 15 OF 28 MEDLINE on STN
TI Oral candidal infection as a sign of **HIV** infection in homosexual men.

L5 ANSWER 16 OF 28 MEDLINE on STN
TI **HIV** testing of surrogate mothers.

L5 ANSWER 17 OF 28 MEDLINE on STN
TI Immune impairments and antibodies to HTLVIII/LAV in asymptomatic male homosexuals in Israel: relevance to the risk of acquired immune deficiency syndrome (AIDS).

L5 ANSWER 18 OF 28 MEDLINE on STN
TI Non-specificity of HTLV-III reactivity in sera from rural Kenya and eastern Zaire.

L5 ANSWER 19 OF 28 MEDLINE on STN
TI Stimulatory and inhibitory influences of **human immunodeficiency**

virus on normal B lymphocytes.

L5 ANSWER 20 OF 28 MEDLINE on STN
TI Normal T cell subsets in homosexual men living in a community without endemic AIDS.

L5 ANSWER 21 OF 28 MEDLINE on STN
TI HTLV: epidemiology and relationship to disease.

L5 ANSWER 22 OF 28 MEDLINE on STN
TI Adult T-cell leukemia/lymphoma in Jamaica and its relationship to human T-cell leukemia/lymphoma virus type I-associated lymphoproliferative disease.

L5 ANSWER 23 OF 28 MEDLINE on STN
TI Unique pattern of HTLV-III (AIDS-related) antigen recognition by sera from African children in Uganda (1972).

L5 ANSWER 24 OF 28 MEDLINE on STN
TI Immunosuppression in homosexual men seronegative for HTLV-III.

L5 ANSWER 25 OF 28 MEDLINE on STN
TI Clinical and immunological findings in HTLV-III infection.

L5 ANSWER 26 OF 28 MEDLINE on STN
TI HTLV-III infection in homosexuals and hemophiliacs in Sweden.

L5 ANSWER 27 OF 28 MEDLINE on STN
TI Diversity of clinical spectrum of HTLV-III infection.

L5 ANSWER 28 OF 28 MEDLINE on STN
TI Risk of nosocomial infection with human T-cell lymphotropic virus III (HTLV-III).

=> d his

(FILE 'HOME' ENTERED AT 13:55:02 ON 04 MAR 2004)

FILE 'USPATFULL' ENTERED AT 13:56:10 ON 04 MAR 2004
E SAXINGER CARL/IN
L1 6 S E3 OR E4

FILE 'WPIDS' ENTERED AT 13:57:03 ON 04 MAR 2004
E SAXINGER C/IN
L2 8 S E3 OR E4

FILE 'MEDLINE' ENTERED AT 13:58:11 ON 04 MAR 2004
E SAXINGER C/AU
L3 71 S E3 OR E4
L4 0 S L3 AND (CCR5 OR CHEMOKINE RECEPTOR?)
L5 28 S L3 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L6 2 S L5 AND (GP120 OR GP160)

=> file uspatful

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.14	17.97

FILE 'USPATFULL' ENTERED AT 13:59:56 ON 04 MAR 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 4 Mar 2004 (20040304/PD)
FILE LAST UPDATED: 4 Mar 2004 (20040304/ED)
HIGHEST GRANTED PATENT NUMBER: US6701528
HIGHEST APPLICATION PUBLICATION NUMBER: US2004045070

CA INDEXING IS CURRENT THROUGH 4 Mar 2004 (20040304/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 4 Mar 2004 (20040304/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2003

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

```
=> s (CCR5 or chemokine receptor?)
          1044 CCR5
          3587 CHEMOKINE
        103134 RECEPTOR?
          1703 CHEMOKINE RECEPTOR?
                 (CHEMOKINE(W)RECEPTOR?)
L7        1938 (CCR5 OR CHEMOKINE RECEPTOR?)

=> s l7 and CCR5
          1044 CCR5
L8        1044 L7 AND CCR5

=> s l8 and CCR5/clm
           163 CCR5/CLM
L9         163 L8 AND CCR5/CLM

=> s l9 and (polypeptide?/clm or peptide?/clm)
         25049 POLYPEPTIDE?/CLM
         22641 PEPTIDE?/CLM
L10         60 L9 AND (POLYPEPTIDE?/CLM OR PEPTIDE?/CLM)

=> d l10,ti,1-60

L10  ANSWER 1 OF 60  USPATFULL on STN
TI     Method and vaccine for the prevention of AIDS

L10  ANSWER 2 OF 60  USPATFULL on STN
TI     Immunogen

L10  ANSWER 3 OF 60  USPATFULL on STN
TI     Method of treating allergen induced airway disease

L10  ANSWER 4 OF 60  USPATFULL on STN
TI     Methods for the modulation of the growth of collateral arteries and/or
       other arteries from preexisting arteriolar connections

L10  ANSWER 5 OF 60  USPATFULL on STN
TI     Method for multiple chemokine receptor screening for antagonists
```

using RAM assay

L10 ANSWER 6 OF 60 USPATFULL on STN
TI Multimeric binding complexes

L10 ANSWER 7 OF 60 USPATFULL on STN
TI Effectors of innate immunity determination

L10 ANSWER 8 OF 60 USPATFULL on STN
TI Chemokine variants and methods of use

L10 ANSWER 9 OF 60 USPATFULL on STN
TI Anti-**CCR5** antibody

L10 ANSWER 10 OF 60 USPATFULL on STN
TI HIV envelope V3-**CCR5** binding site immunogen

L10 ANSWER 11 OF 60 USPATFULL on STN
TI Methods and compositions for treating secondary tissue damage and other inflammatory conditions and disorders

L10 ANSWER 12 OF 60 USPATFULL on STN
TI Immunokine composition and method

L10 ANSWER 13 OF 60 USPATFULL on STN
TI Genostics

L10 ANSWER 14 OF 60 USPATFULL on STN
TI CC **chemokine receptor** 5 DNA, new animal models and therapeutic agents for HIV infection

L10 ANSWER 15 OF 60 USPATFULL on STN
TI Antibody targeting compounds

L10 ANSWER 16 OF 60 USPATFULL on STN
TI Human G-protein chemokine receptor (CCR5) HDGNR10

L10 ANSWER 17 OF 60 USPATFULL on STN
TI High throughput generation of human monoclonal antibody against peptide fragments derived from membrane proteins

L10 ANSWER 18 OF 60 USPATFULL on STN
TI Human monoclonal antibody against coreceptors for human immunodeficiency virus

L10 ANSWER 19 OF 60 USPATFULL on STN
TI G protein coupled receptor agonists and antagonists and methods of activating and inhibiting G protein coupled receptors using the same

L10 ANSWER 20 OF 60 USPATFULL on STN
TI Ligands for FPR class receptors that induce a host immune response to a pathogen or inhibit HIV infection

L10 ANSWER 21 OF 60 USPATFULL on STN
TI Chemokine beta-1 fusion proteins

L10 ANSWER 22 OF 60 USPATFULL on STN
TI Sulfated **CCR5** peptides for HIV-1 infection

L10 ANSWER 23 OF 60 USPATFULL on STN
TI Targeted multivalent macromolecules

L10 ANSWER 24 OF 60 USPATFULL on STN
TI Targeted multivalent macromolecules

L10 ANSWER 25 OF 60 USPATFULL on STN

TI Use of heat shock proteins

L10 ANSWER 26 OF 60 USPATFULL on STN
TI Human G-protein Chemokine Receptor (CCR5) HDGNR10

L10 ANSWER 27 OF 60 USPATFULL on STN
TI Sulfated **CCR5** peptides for HIV-1 infection

L10 ANSWER 28 OF 60 USPATFULL on STN
TI CD4-independent HIV envelope proteins as vaccines and therapeutics

L10 ANSWER 29 OF 60 USPATFULL on STN
TI Immunostimulatory nucleic acids for the treatment of asthma and allergy

L10 ANSWER 30 OF 60 USPATFULL on STN
TI Methods for identifying novel multimeric agents that modulate receptors

L10 ANSWER 31 OF 60 USPATFULL on STN
TI Method and apparatus for increasing the dynamic range and accuracy of binding assays

L10 ANSWER 32 OF 60 USPATFULL on STN
TI Virus-like particles for the induction of autoantibodies

L10 ANSWER 33 OF 60 USPATFULL on STN
TI Polypeptides that bind HIV gp120 and related nucleic acids, antibodies, compositions, and methods of use

L10 ANSWER 34 OF 60 USPATFULL on STN
TI Detection of human immunodeficiency virus using cells transduced with a complex viral vector

L10 ANSWER 35 OF 60 USPATFULL on STN
TI Methods and compositions useful for inhibiting **ccr5**-dependent infection of cells by hiv-1

L10 ANSWER 36 OF 60 USPATFULL on STN
TI Scaffolded fusion polypeptides and compositions and methods for making the same

L10 ANSWER 37 OF 60 USPATFULL on STN
TI Antibody and chemokine constructs and their use in the treatment of infections and immunological diseases

L10 ANSWER 38 OF 60 USPATFULL on STN
TI Cell migration assay

L10 ANSWER 39 OF 60 USPATFULL on STN
TI Pharmaceutical uses and synthesis of nicotinanilide-N-oxides

L10 ANSWER 40 OF 60 USPATFULL on STN
TI Novel **CCR5** epitope and antibodies against it

L10 ANSWER 41 OF 60 USPATFULL on STN
TI Compositions and methods for evaluating viral receptor/co-receptor usage and inhibitors of virus entry using recombinant virus assays

L10 ANSWER 42 OF 60 USPATFULL on STN
TI Early stage multipotential stem cells in colonies of bone marrow stromal cells

L10 ANSWER 43 OF 60 USPATFULL on STN
TI Methods and compositions for treating secondary tissue damage and other inflammatory conditions and disorders

L10 ANSWER 44 OF 60 USPATFULL on STN

TI Non stochastic generation of genetic vaccines

L10 ANSWER 45 OF 60 USPATFULL on STN
TI Transgenic rodents and rodent cell lines expressing HIV co-receptors

L10 ANSWER 46 OF 60 USPATFULL on STN
TI Virus coat protein/receptor chimeras and methods of use

L10 ANSWER 47 OF 60 USPATFULL on STN
TI Compositions and methods for inhibition of HIV-1 infection

L10 ANSWER 48 OF 60 USPATFULL on STN
TI Immunogen

L10 ANSWER 49 OF 60 USPATFULL on STN
TI Virus-like particles for the induction of autoantibodies

L10 ANSWER 50 OF 60 USPATFULL on STN
TI G protein coupled receptor (GPCR) agonists and antagonists and methods of activating and inhibiting GPCR using the same

L10 ANSWER 51 OF 60 USPATFULL on STN
TI Sulfated **CCR5** peptides for HIV-1 infection

L10 ANSWER 52 OF 60 USPATFULL on STN
TI Human G-protein Chemokine receptor (CCR5) HDGNR10

L10 ANSWER 53 OF 60 USPATFULL on STN
TI Method of identifying ligands of biological target molecules

L10 ANSWER 54 OF 60 USPATFULL on STN
TI Human G-protein Chemokine Receptor HDGNR10

L10 ANSWER 55 OF 60 USPATFULL on STN
TI DELAYED PROGRESSION TO AIDS BY A MISSENSE ALLELE OF THE CCR2 GENE

L10 ANSWER 56 OF 60 USPATFULL on STN
TI Method of treating graft rejection using inhibitors of **CCR5** function

L10 ANSWER 57 OF 60 USPATFULL on STN
TI Self-contained system for sustained viral replication

L10 ANSWER 58 OF 60 USPATFULL on STN
TI Method for generating immunogens that elicit neutralizing antibodies against fusion-active regions of HIV envelope proteins

L10 ANSWER 59 OF 60 USPATFULL on STN
TI Methods relating to immunogenic dextran-protein conjugates

L10 ANSWER 60 OF 60 USPATFULL on STN
TI Rapid generation of stable mammalian cell lines producing high levels of recombinant proteins

=> d l10,cbib,ab,clm,33,35,40,58

L10 ANSWER 33 OF 60 USPATFULL on STN
2003:99510 Polypeptides that bind HIV gp120 and related nucleic acids, antibodies, compositions, and methods of use.
Saxinger, Carl, Bethesda, MD, UNITED STATES
Department of Health and Human Services, Rockville, MD (U.S. corporation)
US 2003068615 A1 20030410
APPLICATION: US 2002-84813 A1 20020227 (10)
PRIORITY: US 1999-151270P 19990827 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides, among other things, a polypeptide that binds with the gp120 envelope protein of HIV, in particular HIV-1, under physiological conditions, a nucleic acid that encodes such a polypeptide and can be expressed in a cell, a composition comprising such a polypeptide or nucleic acid or an antibody and a carrier therefor, a composition comprising a solid support matrix to which is attached an above-described polypeptide or an anti-antibody to a specified polypeptide sequence, a method of making an antibody to gp120, and a method of removing HIV from a bodily fluid.

CLM What is claimed is:

1. A **polypeptide** comprising the amino acid sequence YDIXYYXXE, wherein X is any synthetic or naturally occurring amino acid residue, such that the **polypeptide** binds HIV gp120 under physiological conditions, and wherein said **polypeptide** comprises less than about 100 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human **CCR5 chemokine receptor**.

2. The **polypeptide** of claim 1, which comprises less than about 50 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human **CCR5 chemokine receptor**.

3. The **polypeptide** of claim 2, which comprises less than about 25 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human **CCR5 chemokine receptor**.

4. The **polypeptide** of claim 3, which comprises less than about 13 amino acids that are identical to or substantially identical to the amino acid sequence of the human **CCR5 chemokine receptor**.

5. The **polypeptide** of claim 4, which consists essentially of YDIXYYXXE.

6. The **polypeptide** of any of claims 1-5, which comprises the amino acid sequence YDIN*YYT*S*E, wherein N* is asparaginyl or a synthetic or naturally occurring substitute therefor, T* is threoninyl or a synthetic or naturally occurring substitute therefor, and S* is serinyl or a synthetic or naturally occurring substitute therefor.

7. The **polypeptide** of claim 6, wherein N* is asparaginyl, T* is threoninyl, and S* is serinyl.

8. The **polypeptide** of any of claims 1-6, comprising the amino acid sequence M*D*YQ*V*S*SP*IYDIN*YYT*S*E, wherein each letter indicates the standard amino acid residue designated by that letter, and a letter followed directly by an * indicates that any synthetic or naturally occurring amino acid can occupy that position.

9. The **polypeptide** of claim 8, wherein said letter followed directly by an * indicates the amino acid residue represented by the letter or a synthetic or naturally occurring conservative or neutral amino acid substitution therefor.

10. The **polypeptide** of claim 9, wherein said amino acid sequence is MDYQVSSPIYDINYYTSE.

11. A **polypeptide** comprising the amino acid sequence XEXIXIYXXXNYXXX, wherein X is any synthetic or naturally occurring amino acid, such that the **polypeptide** binds HIV gp120 under physiological conditions, and wherein said **polypeptide** less than about 100 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human CXCR4 **chemokine receptor**.

12. The **polypeptide** of claim 11, which comprises less than about 50 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human CXCR4 **chemokine receptor**.

13. The **polypeptide** of claim 11, which comprises less than 25

contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human CXCR4 **chemokine receptor**.

14. The **polypeptide** of claim 13, which consists essentially of EXIXIYXXXNY.

15. The **polypeptide** of any of claims 11-14, which comprises the amino acid sequence M*EG*IS*IYT*S*D*NYT*E*E*, wherein each letter indicates the standard amino acid residue designated by that letter, and each letter followed directly by an * indicates the amino acid residue represented by the letter or a synthetic or naturally occurring conservative or neutral amino acid substitution therefor.

16. The **polypeptide** of claim 15, wherein said amino acid sequence M*EG*IS*IYT*S*D*NYT*E*E* is M*EGISIYTSDNYT*E*E*.

17. A **polypeptide** comprising the amino acid sequence EHQAFLQFS, such that the **polypeptide** binds with HIV gp120 under physiological conditions and wherein said **polypeptide** comprises less than about 100 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human STRL33 **chemokine receptor**.

18. The **polypeptide** of claim 17, which comprises less than about 50 contiguous amino acid that are identical to or substantially identical to the amino acid sequence of the human STRL33 **chemokine receptor**.

19. The **polypeptide** of claim 18, which comprises less than about 25 contiguous amino acids that are identical to or substantially identical to the amino acid sequence of the human STRL33 **chemokine receptor**.

20. The **polypeptide** of claim 19, which consists essentially of the sequence EHQAFLQFS.

21. A **polypeptide** comprising at least a portion or all of an amino acid sequence selected from the group consisting of LPPLYSLVFIFGFVGNML, QWDFGNTMCQLLTGLYFIGFFS, SQYQFWKNFQTLKIVILG, APYNIVLLLNTFQEFFGLNNCS, and YAFVGEKFRNYLLVFFQK, wherein the **polypeptide** binds with HIV gp120 under physiological conditions and comprises less than about 100 amino acid residues that are identical to or substantially identical to the amino acid sequence of the human **CCR5 chemokine receptor**.

22. A **polypeptide** comprising at least a portion or all of an amino acid sequence selected from the group consisting of LLLTIPDFIFANVSEADD (165-182), VVFQFQHIMVGLILPGIV (197-214), and IDSFILLEIIKQGGCEFEN (261-278), wherein the **polypeptide** binds with HIV gp120 under physiological conditions and comprises less than about 100 amino acid residues that are identical to or substantially identical to the amino acid sequence of the human CXCR4 **chemokine receptor**.

23. A **polypeptide** comprising at least a portion or all of an amino acid sequence selected from the group consisting of LVISIFYHKLQSLTDVFL (53-70), PFWAYAGIHEWVFGQVMC (85-102), EAISTVVLATQMTLGFFL (185-202), LTMIVCYSVIIKTLLHAG (205-222), MAVFLLTQMPFNLMKFIRSTHW (237-258), HWEYYAMTSFHYTIMVTE (257-274), ACLNPVLYAFVSLKFRKN (281-298) and SKTFSASHNVEATSMFQL (325-342), wherein the **polypeptide** binds with-HIV gp120 under physiological conditions and comprises less than about 100 amino acid residues that are identical to or substantially identical to the amino acid sequence of the human STRL33 **chemokine receptor**.

24. A **polypeptide** comprising at least a portion of or all of an amino acid sequence selected from the group consisting of DTYICEVED, EEVQLLVFGLTANSD, THLLQGQSLTLTLES, and GEQVEFSFPLAFTVE, wherein the **polypeptide** binds with HIV gp120 under physiological conditions and wherein the **polypeptide** comprises less than about 100 amino acids that are identical to or substantially identical to the amino acid sequence of the human CD4 cell-surface protein.

25. A **polypeptide** of any of claims 21-24, which comprises all of the amino acid sequence and 0 to about 6 conservative or neutral amino acid substitutions.

26. The **polypeptide** of claim 25, comprising 0 amino acid substitutions.

27. The **polypeptide** of any of claims 21-26, which comprises less than about 50 amino acids that are identical to or substantially identical to a protein that naturally has the amino acid sequence.

28. The **polypeptide** of any of claims 21-26, which comprises less than about 25 amino acids that are identical to or substantially identical to a protein that naturally has the amino acid sequence.

29. The **polypeptide** of any of claims 1-28, wherein said **polypeptide** further comprises a pharmaceutically acceptable substituent.

30. A composition comprising the **polypeptide** of any of claims 1-28, and a carrier.

31. A nucleic acid encoding the **polypeptide** of any of claims 1-28, wherein said nucleic acid can be expressed in a cell.

32. The nucleic acid of claim 31, further comprising a nucleic acid sequence that encodes a signal sequence, wherein said signal sequence is translated as a fusion protein with the **polypeptide** to form a signal sequence-**polypeptide** fusion, and wherein said signal sequence can cause secretion of at least the **polypeptide** out of a cell in which the nucleic acid is expressed.

33. A vector comprising the nucleic acid of claim 31 or 32.

34. A method of making an antibody, which method comprises administering an immunogenic amount of a **polypeptide** of any of claims 1-28 or a nucleic acid of any of claims 31 or 33 to an animal.

35. A method of prophylactically or therapeutically treating HIV infection in a mammal in need thereof, which method comprises administering to said mammal an effective amount of a **polypeptide** of any of claims 1-28, a nucleic acid of any of claims 31-33, or an anti-antibody to a **polypeptide** of any of claims 1-28.

36. A method of making an antibody that binds to a gp120 envelope protein of a human immunodeficiency virus-1 (HIV-1), said method comprising: (a) labeling a **polypeptide** of any of claims 1-28 to obtain a labeled compound, (b) providing a library of synthetic **peptides**, wherein said library consists of a multiplicity of synthetically-produced **polypeptides** that are homologous to a continuous region of an HIV-1 gp120 envelope protein, wherein each **polypeptide** of said library is substantially isolated from every other **polypeptide** of said library and is located in a known position, (c) individually contacting each **polypeptide** with said labeled compound such that a portion of the labeled compound can bind with the **polypeptide**, thereby producing a bound population of each **polypeptide** and an unbound population of each **polypeptide**, (d) removing substantially all of the unbound labeled compound from the position occupied by each **polypeptide**, (e) measuring the amount of labeled compound that remains co-localized with each **polypeptide**, to determine the quantity of labeled compound bound by each **polypeptide**, (f) evaluating the amount of labeled compound bound by each **polypeptide** to identify a portion of the HIV-1 gp120 envelope protein that binds to an (HIV-1)-receptor selected from the group consisting of **CCR5**, CXCR4, STRL33, and CD4, (g) providing an immunizing compound comprising a **polypeptide** comprising an amino acid sequence that is homologous to said portion of the HIV-1 gp120 envelope protein, (h)

inserting an immunogenic quantity of said immunizing compound into an animal to cause said animal to produce an antibody that binds with said portion of the HIV-1 gp120 envelope protein.

37. The method of claim 36, wherein said labeled compound comprises a moiety selected from the group consisting of a radioactive atom, an enzyme, a polyhistidinyl moiety, and an antigen that is specifically recognized by a standard antibody.

38. The method of claim 36 or 37, wherein said library consists of a multiplicity of synthetically-produced **polypeptides** that are identical to a continuous region of an HIV-1 gp120 envelope protein.

39. The method of any of claims 36-38, wherein said **polypeptides** contain at least about 6 amino acid residues and no more than about 45 amino acid residues.

40. The method of claim 39, wherein said **polypeptides** contain no more than about 30 amino acid residues.

41. The method of any of claims 36-40, wherein said library comprises a multiplicity of **polypeptides** of identical lengths.

42. The method of any of claims 36-41, wherein said library comprises a multiplicity of **polypeptides** that are homologous to a region of the HIV-1 gp120 envelope protein and have an offset of n amino acid residues, wherein n is an integer of at least 1 and is not greater than the product of length of the longest **polypeptide** measured in amino acid residues and 1.5.

43. The method of claim 42, wherein said offset is not greater than the product of length of the longest **polypeptide** measured in amino acid residues and 1.0.

44. The method of claim 42, wherein said offset is not greater than the product of length of the longest **polypeptide** measured in amino acid residues and 0.5.

45. The method of claim 42, wherein said offset is not greater than 30.

46. The method of claim 42, wherein said offset is not greater than 15.

47. The method of claim 42, wherein said offset is not greater than 4.

48. The method of any of claims 36-47, wherein each **polypeptide** is bound to a solid support and is located in a vessel that enables each **polypeptide** to be covered in a liquid that does not contact any other oligonucleotide of the library.

49. The method of claim 48, wherein each **polypeptide** is bound to a bead in a vessel or is bound to the well of a multi-well assay plate.

50. The method of claim 36, wherein said step of removing substantially all of the unbound labeled compound comprises the additional steps of (i) removing a liquid containing said unbound labeled compound from a solid substrate to which an **polypeptide** of the library is bound, (ii) applying a quantity of wash-liquid to said solid substrate that is sufficient to cover any portion of said solid substrate or a vessel containing said solid substrate that has been contacted by said labeled compound, and (iii) removing said wash-liquid.

51. The method of any of claims 36-50, wherein said immunizing compound comprises an adjuvant or wherein said **polypeptide** comprising an amino acid sequence that is homologous to said portion of the HIV gp120 envelope protein is conjugated to a known immunogen.

52. The method of any of claims 36-51, wherein said method is performed in a mammal belonging to a group selected from the group consisting of rodents, canines, felines, and ruminants.

53. The immunizing compound of step (g) of the method of any of claims 36-52.

54. An antibody produced by the method of any of claims 36-53.

55. A method of removing HIV from a bodily fluid of a mammal, which method comprises extra-corporeally contacting said bodily fluid with a solid support to which is attached a **polypeptide** of any of claims 1-28 or an anti-antibody to a **polypeptide** of any of claims 1-78, or the antibody of claim 54.

L10 ANSWER 35 OF 60 USPATFULL on STN
2003:70966 Methods and compositions useful for inhibiting **ccr5**-dependent infection of cells by hiv-1.
Barbas, Carlos F., Solana Beach, CA, UNITED STATES
Steinberger, Peter, Wein, AUSTRIA
US 2003049251 A1 20030313
APPLICATION: US 2001-913238 A1 20010808 (9)
WO 2000-EP12419 20001208
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for inhibiting, diminishing, preventing or treating pathogenic infection of cells comprising expressing a recombinant antibody protein fused to an intracellular anchor means, wherein said antibody is specific for a surface receptor of said cells necessary for pathogenic infection, wherein said antibody is suitably selected from **CCR5** and CXCR4 specific antibodies. A recombinant antibody protein fused to an intracellular anchor means which is specific for a surface receptor necessary for pathogenic infection, but suitably elected from **CCR5** and CXCR4 specific antibodies and humanized antibodies therefrom. A recombinant antibody that immunoreacts with **CCR5** or CXCR4 surface receptor. Peptides comprising at least YTSF or YTSQ sequence for use in a vaccine or an immunogenic composition intended to control, prevent, diminish or treat HIV infections. An antiidiotypic antibody mimicking **CCR5** or CXCR4 epitopes raised from anti-**CCR5** and anti-CXCR4 antibodies.

CLM What is claimed is:

1. A method for inhibiting, diminishing, preventing or treating pathogenic infection of cells comprising expressing a recombinant antibody protein fused to an intracellular anchor means, wherein said antibody is specific for a surface receptor of said cells necessary for pathogenic infection.

2. The method of claim 1, wherein said antibody is selected from **CCR5** and CXCR4 specific antibodies.

3. The method of claim 2, wherein said antibody is a scFv-fusion protein comprising a scFv domain that immunoreacts with **CCR5** or CXCR4 fused to an intracellular anchor means.

1 The method of claim 3 wherein said scFv-fusion protein comprises amino acid residues selected from SEQ ID NO:1 to NO: 4.

4. The method of claim 1 wherein said intracellular anchor means is an endoplasmic reticulum (ER) retention **peptide** domain.

5. The method of claim S wherein said ER retention **peptide** is KDEL.

6. The method of claim 1 wherein said expression comprises in vivo or ex vivo transformation of **CCR5**- or CXCR4- bearing cell.

7. The method of claim 7, wherein stem cells are transformed, more

specifically hematopoietic cells.

8. The method of any of the preceding claims, wherein **CCR5** and CXCR4 specific antibodies are co-expressed in cells.

9. The method of any of the preceding claims 1-8, wherein said antibody is humanized.

10. A recombinant antibody protein fused to an intracellular anchor means which is specific for a surface receptor necessary for pathogenic infection.

11. The antibody of claim 11, wherein said antibody is selected from **CCR5** and CXCR4 specific antibodies.

12. The antibody of claim 12, wherein said antibody is a scFv-fusion protein comprising a scFv domain that immunoreacts with **CCR5** or CXCR4 fused to an intracellular anchor mean.

13. The antibody of claim 13, wherein said scFv-fusion protein comprises amino acid residues selected from SEQ ID NO:1 to NO: 4.

14. The antibody of claim 11, wherein said intracellular anchor mean is an endoplasmic reticulum (ER) retention **peptide** domain.

15. The antibody of claim 15 wherein said ER retention **peptide** is KDEL.

16. The antibody of any of the preceding claims 11-14, wherein said antibody is humanized.

17. A recombinant antibody that immunoreacts with **CCR5** or CXCR4.

18. The antibody of claim 18 wherein said antibody is humanized.

19. The antibody of claim 18 wherein said antibody is a single chain antibody (scFv).

20. The antibody of claim 1 wherein said antibody comprises amino acid residues selected from SEQ ID NO:1 to NO:4.

21. A polynucleotide that encodes an antibody according to any of the preceding claims 11 to 20.

22. A viral expression system encoding a polynucleotide of claim 22.

23. **Peptides** comprising at least YTSE or YTSQ sequence for use in a vaccine or an immunogenic composition intended to control, prevent, diminish or treat HIV infections.

24. An antiidiotypic antibody mimicking **CCR5** or CXCR4 epitopes raised from anti-**CCR5** and anti-CXCR4 antibodies.

L10 ANSWER 40 OF 60 USPATFULL on STN
2003:3405 Novel **CCR5** epitope and antibodies against it.
Lopalco, Lucia, Milano, ITALY
US 2003003440 A1 20030102
APPLICATION: US 2001-805375 A1 20010314 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a novel antigenic/immunogenic peptide derived from the **CCR5 chemokine receptor**, useful in the treatment of HIV infection.
CLM What is claimed is:
1. Immunogenic **peptide** derived from the **CCR5 chemokine receptor**, having the following sequence: CYAAAQWDFGNTMCQ.

2. Monoclonal or polyclonal antibodies against the **peptide** of claim 1.

3. A pharmaceutical composition comprising the **peptide** of claim 1 or the antibodies of claim 2.

4. A pharmaceutical composition containing the **peptide** according to claim 3, which is in form of vaccine.

5. A method for inducing immunity against the **CCR5** protein which comprises administering to a human subject an effective amount of the immunogenic **peptide** of claim 1 or of the antibodies of claim 2.

6. A method according to claim 3, wherein the subject is a patient infected by HIV or he has been exposed, or is at risk of exposure, to HIV.

7. A method to inhibit or prevent HIV infections which comprises inducing immunity against **CCR5** receptor by administering to a patient infected by HIV or to a subject exposed, or at risk of exposure, to HIV, an effective amount of the immunogenic **peptide** of claim 1 or of the antibodies of claim 2.

8. A method of treating diseases in the etiopathogenesis of which Mip1ξ/**CCR5** binding is involved, which comprises administering to a subject in need of such a treatment an antibody according to claim 2.

9. A method according to claim 8, wherein said diseases are selected from inflammation and graft versus host diseases.

10. A method for detecting an antibody to **CCR5** in a sample, which comprises (a) incubating said sample with the **peptide** of claim 1, or a derivative thereof, and (b) detecting the formation of a complex between said antibody and **peptide**.

11. The use of the antibodies of claim 2 to prevent chemokine Mip1β/**CCR5** binding.

L10 ANSWER 58 OF 60 USPATFULL on STN
2002:17437 Method for generating immunogens that elicit neutralizing antibodies against fusion-active regions of HIV envelope proteins.
Wild, Carl T., Gaithersburg, MD, UNITED STATES
Allaway, Graham P., Darnestown, MD, UNITED STATES
US 2002010317 A1 20020124
APPLICATION: US 2001-809060 A1 20010316 (9)
PRIORITY: US 2000-189981P 20000317 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The current invention relates to methods of generating immunogens that elicit broadly neutralizing antibodies which target regions of viral envelope proteins such as the gp 120/gp41 complex of HIV-1. More specifically, the current invention involves using stabilizing peptides modeling the α-helical regions of the ectodomain of the HIV-1 transmembrane protein to stabilize fusion-active intermediate structures which can be used as vaccine immunogens.

CLM What is claimed is:
1. An immunogenic composition, comprising: (a) at least one viral envelope protein or fragment thereof exterior to a viral membrane, and (b) an amount of at least one stabilizing **peptide** effective to disrupt formation of one or more structural intermediates necessary for viral fusion and entry, and, optionally, (c) at least one viral cell surface receptor or fragment thereof, wherein the stabilizing **peptide** is capable of associating with the envelope protein or fragment thereof to form a stabilized, fusion-active structure.

2. The immunogenic composition of claim 1, wherein the at least one viral envelope protein or fragment thereof is a glycoprotein.

3. The immunogenic composition of claim 2, wherein the glycoprotein is the HIV-1 gp41/gp120 complex.

4. The immunogenic composition of claim 1, wherein the at least one viral cell surface receptor or fragment thereof is an HIV-1 cell surface receptor or a soluble fragment thereof.

5. The immunogenic composition of claim 4, wherein the HIV-1 cell surface receptor or fragment thereof is CD4.

6. The immunogenic composition of claim 1, wherein the at least one stabilizing **peptide** is selected from the group consisting of: a **peptide** comprising SEQ ID NO: 1, a **peptide** comprising a fragment of SEQ ID NO:1, a **peptide** comprising SEQ ID NO:2, a **peptide** comprising a fragment of SEQ ID NO:2, a **peptide** comprising SEQ ID NO:3, a **peptide** comprising a fragment of SEQ ID NO:3, a **peptide** comprising SEQ ID NO:4, a **peptide** comprising a fragment of SEQ ID NO:4, a **peptide** comprising SEQ ID NO:5, a **peptide** comprising a fragment of SEQ ID NO:5, a **peptide** comprising SEQ ID NO:6, a **peptide** comprising a fragment of SEQ ID NO:6, a **peptide** comprising SEQ ID NO:7, a **peptide** comprising a fragment of SEQ ID NO:7, a **peptide** comprising SEQ ID NO:9, a **peptide** comprising a fragment of SEQ ID NO:9, a **peptide** comprising any combination of SEQ ID NOS:1-7 and 9, a **peptide** comprising any combination of fragments of SEQ ID NOS:1-7 and 9, a **peptide** functionally equivalent to any one of SEQ ID NOS:1-7 and 9, a homolog of any of SEQ ID NOS:1-7 and 9 and an analog of any of SEQ ID NOS:1-7 and 9.

7. An immunogenic composition, produced by a process comprising: (a) incubating at least one non-infectious viral particle with a concentration of one or more stabilizing **peptides** effective to disrupt formation of one or more structural intermediates necessary for viral fusion and entry to obtain a mixture; and (b) adding a soluble form of one or more viral cell surface receptors or a fragment thereof to the mixture, whereby an immunogenic composition is created.

8. The immunogenic composition of claim 7, comprising at least one viral envelope protein or fragment thereof exterior to the viral membrane, at least one viral cell surface receptor or fragment thereof and an amount of at least one stabilizing **peptide** effective to disrupt formation of one or more structural intermediates necessary for viral fusion and entry.

9. A method of preparing an immunogenic composition, comprising: (a) incubating at least one non-infectious viral particle having at least one surface envelope protein or fragment thereof exterior to the viral membrane with an amount of at least one stabilizing **peptide** effective to disrupt formation of one or more structural intermediates necessary for viral fusion and entry to obtain a protein/**peptide** first mixture; (b) adding a soluble form of at least one cell surface receptor or fragment thereof to the protein/**peptide** first mixture to create a second mixture; and (c) isolating the resulting fusion-active protein/**peptide** complex from the second mixture.

10. The method of claim 9, wherein the protein/**peptide** complex is isolated from the second mixture by treating the second mixture with a detergent.

11. The method of claim 9, further comprising: (d) purifying the isolated protein/**peptide** complex.

12. The method of claim 11, wherein the isolated protein/**peptide** complex is purified by affinity chromatography, ion exchange

chromatography, ultracentrifugation or gel filtration.

13. The method of claim 9, wherein the at least one surface envelope protein or fragment thereof is the HIV-1 gp41/gp120 complex.

14. The method of claim 9, wherein the at least one cell surface receptor or fragment thereof is an HIV-1 cell surface receptor.

15. The method of claim 14, wherein the HIV-1 cell surface receptor is CD4.

16. The method of claim 9, wherein the at least one stabilizing **peptide** is selected from the group consisting of: a **peptide** comprising SEQ ID NO: 1, a **peptide** comprising a fragment of SEQ ID NO:1, a **peptide** comprising SEQ ID NO:2, a **peptide** comprising a fragment of SEQ ID NO:2, a **peptide** comprising SEQ ID NO:3, a **peptide** comprising a fragment of SEQ ID NO:3, a **peptide** comprising SEQ ID NO:4, a **peptide** comprising a fragment of SEQ ID NO:4, a **peptide** comprising SEQ ID NO:5, a **peptide** comprising a fragment of SEQ ID NO:5, a **peptide** comprising SEQ ID NO:6, a **peptide** comprising a fragment of SEQ ID NO:6, a **peptide** comprising SEQ ID NO:7, a **peptide** comprising a fragment of SEQ ID NO:7, a **peptide** comprising SEQ ID NO:9, a **peptide** comprising a fragment of SEQ ID NO:9, a **peptide** comprising any combination of SEQ ID NOS:1-7 and 9, a **peptide** comprising any combination of fragments of SEQ ID NOS:1-7 and 9, a **peptide** functionally equivalent to any one of SEQ ID NOS:1-7 and 9, a homolog of any of SEQ ID NOS:1-7 and 9 and an analog of any of SEQ ID NOS:1-7 and 9.

17. The method of claim 9, wherein the at least one cell surface receptor is obtained from a cell line that expresses CD4, an appropriate **chemokine receptor**, or a combination thereof.

18. The method of claim 17, wherein the appropriate **chemokine receptor** is selected from the group consisting of: **CCR5**, CXCR4 or a mixture thereof.

19. A method of preparing an immunogenic composition, comprising: (a) incubating cells expressing at least one HIV envelope protein or fragment thereof exterior to the viral membrane with an amount of at least one stabilizing **peptide** effective to disrupt formation of one or more structural intermediates necessary for viral fusion and entry to obtain a protein/**peptide** first mixture; (b) adding a soluble form of at least one cell surface receptor or fragment thereof to the protein/**peptide** first mixture to create a second mixture; (c) isolating the resulting fusion-active protein/**peptide** complex from the second mixture by treating the second mixture with a lysis buffer; and (d) purifying the protein/**peptide** complex.

20. The method of claim 19, wherein the protein/**peptide** complex is purified by affinity chromatography, ion exchange chromatography, ultracentrifugation or gel filtration.

21. The method of claim 19, wherein the cells expressing the at least one HIV envelope protein or fragment thereof are cells infected with a recombinant vaccinia virus expressing the HIV-1 envelope protein or fragment thereof.

22. The method of claim 19, wherein the at least one stabilizing **peptide** is selected from the group consisting of: a **peptide** comprising SEQ ID NO: 1, a **peptide** comprising a fragment of SEQ ID NO:1, a **peptide** comprising SEQ ID NO:2, a **peptide** comprising a fragment of SEQ ID NO:2, a **peptide** comprising SEQ ID NO:3, a **peptide** comprising a fragment of SEQ ID NO:3, a **peptide** comprising SEQ ID NO:4, a **peptide** comprising a fragment of SEQ ID NO:4, a **peptide** comprising SEQ ID NO:5, a **peptide** comprising a fragment of SEQ ID

NO:5, a **peptide** comprising SEQ ID NO:6, a **peptide** comprising a fragment of SEQ ID NO:6, a **peptide** comprising SEQ ID NO:7, a **peptide** comprising a fragment of SEQ ID NO:7, a **peptide** comprising SEQ ID NO:9, a **peptide** comprising a fragment of SEQ ID NO:9, a **peptide** comprising any combination of SEQ ID NOS:1-7 and 9, a **peptide** comprising any combination of fragments of SEQ ID NOS:1-7 and 9, a **peptide** functionally equivalent to any one of SEQ ID NOS:1-7 and 9, a homolog of any of SEQ ID NOS:1-7 and 9 and an analog of any of SEQ ID NOS:1-7 and 9.

23. The method of claim 19, wherein the at least one cell surface receptor or fragment thereof is obtained from a cell line that expresses CD4, an appropriate **chemokine receptor**, or a combination thereof.

24. The method of claim 23, wherein the appropriate **chemokine receptor** is selected from the group consisting of: **CCR5**, CXCR4 or a mixture thereof.

25. The method of claim 19, wherein the at least one HIV envelope protein or fragment thereof is a recombinant form of the HIV-1 gp41 ectodomain.

26. The method of claim 19, wherein the protein/**peptide** complex is formed in the presence of a denaturant.

27. The method of claim 19, wherein the cells expressing the at least one HIV envelope protein or fragment thereof are cells transformed with a vector expressing the HIV-1 envelope protein or fragment thereof.

28. A method of preparing vaccine immunogens comprising isolating gp41 or a fragment thereof and introducing structure disrupting mutations into specific positions in the structural regions of gp41 or fragment thereof resulting in the production of a fusion-active vaccine immunogen.

29. The method of claim 28, wherein the mutations comprise substitutions of the invariant residues within the 4-3 heptad repeats found in each helical region with residues incompatible with the formation of α-helical secondary structure.

30. A product formed by the method of claim 9.

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L10 ANSWER 1 OF 60 USPATFULL on STN
2004:57031 Method and vaccine for the prevention of AIDS.
Green, Lorrence H., Westbury, NY, UNITED STATES
US 2004043033 A1 20040304
APPLICATION: US 2001-846687 A1 20010501 (9)
PRIORITY: US 2000-200983P 20000501 (60)
DOCUMENT TYPE: Utility; APPLICATION.

AB The present invention is directed to a method of inducing the body to produce an antibody against the region of the **CCR5** receptor in wild type individuals, that is affected by the delta 32 deletion and vaccines for producing said antibody. The antibody is produced is by treating the individual using a vaccine consisting of a polypeptide and its derivatives.

CLM What is claimed is:
1. A method of inducing the body to produce an antibody against the region of the **CCR5** receptor in wild type individuals, that is affected by the delta 32 deletion comprising using a vaccine including a **polypeptide** having the following sequence:

Tyr-Ser-Gln-Tyr-Gln-Phe-Trp-Lys-Asn-Phe-Gln-Thr-

Leu-LysIle-V al-Ile-Leu-Gly-Leu-V al-Leu-Pro-Leu-

Leu-V al-Met-V al-Ile-Cys-TyrSer-Gly-Ile-Leu-Lys-

Thr-Leu-Leu-Arg-Cys-Arg-Asn-Glu-Lys-Lys-Arg.

2. The method according to claim 1 wherein the vaccine is a derivative of said **polypeptide**.

3. The method according to claim 1 wherein said vaccine produces an antibody bound to the **CCR5** site.

4. A method of treating a patient infected with HIV comprising using a vaccine including a **polypeptide** having the following sequence:

Tyr-Ser-Gln-Tyr-Gln-Phe-Trp-Lys-Asn-Phe-Gln-Thr-

Leu-LysIle-V al-Ile-Leu-Gly-Leu-Val-Leu-Pro-Leu-

Leu-Val-Met-V al-Ile-Cys-TyrSer-Gly-lle-Leu-Lys-

Thr-Leu-Leu-Arg-Cys-Arg-Asn-Glu-Lys-Lys-Arg wherein said vaccine produces an antibody against the region of the **CCR5** receptor in wild type individuals, that is affected by the delta 32 deletion.

5. The method according to claim 2 wherein the vaccine is a derivative of said **polypeptide**.

6. A vaccine for producing an antibody against the region of the **CCR5** receptor in wild type individuals, that is affected by the delta 32 deletion comprising a **polypeptide** having the following sequence:

Tyr-Ser-Gln-Tyr-Gln-Phe-Trp-Lys-Asn-Phe-Gln-Thr-

Leu-LysIle-Val-Ile-Leu-Gly-Leu-V al-Leu-Pro-Leu-

Leu-Val-Met-Val-Ile-Cys-TyrSer-Gly-Ile-Leu-Lys-

Thr-Leu-Leu-Arg-Cys-Arg-Asn-Glu-Lys-Lys-Arg.

7. A method of vaccination comprising providing a **polypeptide** that causes a body to generate antibodies in response to said **polypeptide**, said antibodies inactivating viral receptors.

8. The method according to claim 7 wherein said **polypeptide** has the following sequence:

Tyr-Ser-Gln-Tyr-Gln-Phe-Trp-Lys-Asn-Phe-Gln-Thr-

Leu-LysIle-Val-Ile-Leu-Gly-Leu-V al-Leu-Pro-Leu-

Leu-Val-Met-Val-IIe-Cys-TyrSer-Gly-Ile-Leu-Lys-

Thr-Leu-Leu-Arg-Cys-Arg-Asn-Glu-Lys-Lys-Arg.

9. The method according to claim 8 wherein the vaccine is a derivative of said **polypeptide**.

10. The method according to claim 9 wherein said vaccine produces an antibody bound to the **CCR5** site.

L10 ANSWER 5 OF 60 USPATFULL on STN
2004:31148 Method for multiple **chemokine receptor** screening for antagonists using RAM assay.

Wei, Zheng, Redwood City, CA, UNITED STATES
Chemocentryx. (U.S. corporation)
US 2004023286 A1 20040205
APPLICATION: US 2003-630180 A1 20030730 (10)
PRIORITY: US 2001-296682P 20010607 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to a modified cell migration assay allowing for improved identification and discrimination of **chemokine receptor** antagonists from non-specific migration blockers.
CLM What is claimed is:

1. A method for identifying a chemoattractant receptor antagonist, comprising: incubating a cell population comprising first and second chemoattractant receptors; contacting the cell population with an inhibitory concentration of a ligand for the first chemoattractant receptor; contacting the cell population with an inhibitory concentration of a ligand for the second chemoattractant receptor; contacting the cell population with a candidate antagonist; assaying migration of the cell population, wherein migration identifies the candidate antagonist as an antagonist of at least one of the first and second chemoattractant receptors; and determining whether an identified antagonist is an antagonist for one of the first chemoattractant receptors, the second chemoattractant receptor, or both.

2. The method of claim 1, wherein the step of contacting the cell population with a candidate antagonist comprises contacting the cell population with at least two candidate antagonists.

3. The method of claim 1, wherein the candidate antagonist is a **peptide**, **peptide**-like molecule, non-peptidyl organic compound, inorganic compound, nucleic acid or antibody.

4. The method of claim 1, wherein the inhibitory concentration of the ligand for the first chemoattractant receptor inhibits cell migration greater than or equal to about 50% of maximal ligand-activated cell migration.

5. The method of claim 1, wherein the inhibitory concentration of the ligand for the first chemoattractant receptor inhibits cell migration greater than or equal to about 95% of maximal ligand-activated cell migration.

6. The method of claim 1, wherein the inhibitory concentration of the ligand for the first chemoattractant receptor inhibits cell migration greater than or equal to about 100% of maximal ligand-activated cell migration.

7. The method of claim 1, wherein the inhibitory concentration of the ligand for the second chemoattractant receptor inhibits cell migration greater than or equal to about 50% of maximal ligand-activated cell migration.

8. The method of claim 1, wherein the inhibitory concentration of the ligand for the second chemoattractant receptor inhibits cell migration greater than or equal to about 95% of maximal ligand-activated cell migration.

9. The method of claim 1, wherein the inhibitory concentration of the ligand for the second chemoattractant receptor inhibits cell migration greater than or equal to about 100% of maximal ligand-activated cell migration.

10. The method of claim 1, wherein the first and second chemoattractant receptors are each independently a **chemokine receptor**.

11. The method of claim 10, wherein the **chemokine receptor** is

selected from the group consisting of CCR, CXCR, CX3CR, and XCR classes of **chemokine receptors**.

12. The method of claim 11, wherein the **chemokine receptors** are CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CCR1, CCR2, CCR3, CCR4, **CCR5**, CCR6, CCR7, CCR8, CCR9, CCR10, CCR11, CX3CR1 or XCR1.

13. The method of claim 1, wherein the ligand for the first chemoattractant receptor is a chemokine.

14. The method of claim 13, wherein the chemokine is selected from the group consisting of CCR, CXCR, and CX3CR.

15. The method of claim 14, wherein the chemokine is IL-8, GCP-2, Gro α, Gro β, Gro γ, ENA-78, PBP, MIG, IP-10, I-TAC, SDF-1α, BLC, MIP-1α, MIP-1β, RANTES, HCC-1, HCC-2, HCC-3, HCC-4, MCP-1, MCP-2, MCP-3, MCP-4, eotaxin-1, eotaxin-2, TARC, MDC, MIP-3α, MIP-3β, 6Ckine, I-309, TECK, lymphotactin, fractalkine, TCA-4, Exodus-2, Exodus-3, or CKβ-11.

16. The method of claim 1, wherein the ligand for the second chemoattractant receptor is a chemokine.

17. The method of claim 16, wherein the chemokine is selected from the group consisting of CCR, CXCR, and CX3CR.

18. The method of claim 17, wherein the chemokine is IL-8, GCP-2, Gro α, Gro β, Gro γ, ENA-78, PBP, MIG, IP-10, I-TAC, SDF-1α, BLC, MIP-1α, MIP-1, RANTES, HCC-1, HCC-2, HCC-3, HCC-4, MCP-1, MCP-2, MCP-3, MCP-4, eotaxin-1, eotaxin-2, TARC, MDC, MIP-3α, MIP-3β, 6Ckine, 1-309, TECK, lymphotactin, fractalkine, TCA-4, Exodus-2, Exodus-3, or CKβ-11.

19. The method of claim 1, wherein the ligands for the first and the second **chemokine receptors** are added simultaneously.

20. The method of claim 1, wherein the ligands for the first and the second **chemokine receptors** are added in series.

21. The method of claim 1, wherein the candidate antagonist is contacted before at least one of the ligands.

22. The method of claim 1, wherein assaying migration comprises measuring a signal.

23. The method of claim 22, wherein the signal is a fluorescent signal.

24. The method of claim 1, wherein assaying comprises counting cells using a microscope.

25. The method of claim 1, wherein assaying comprises labeling cells with a marker.

26. The method of claim 25, wherein the marker is a dye or a radioactive label.

27. The method of claim 1, wherein determining is performed by a method comprising steps of: incubating a first cell population comprising first chemoattractant receptor with a candidate antagonist; incubating a second cell population comprising second chemoattractant receptor with the candidate antagonist; contacting the first cell population with an inhibitory concentration of a ligand for the first chemoattractant receptor; contacting the second cell population with an inhibitory concentration of a ligand for the second chemoattractant receptor; and assaying cell migration of the first and the second cell population,

wherein cell migration identifies the candidate antagonist as an antagonist of either the first or the second chemoattractant receptor.

28. A method for identifying a chemoattractant receptor antagonist, comprising: incubating a first cell population and a second cell population, wherein the first cell population comprises a first chemoattractant receptor and wherein the second cell population comprises a second chemoattractant receptor; contacting the first and the second cell populations with an inhibitory concentration of a ligand for the first chemoattractant receptor; contacting the first and the second cell populations with an inhibitory concentration of a ligand for the second chemoattractant receptor; contacting the first and the second cell populations with a candidate antagonist; assaying migration of the first and the second cell populations, wherein migration identifies the candidate antagonist as an antagonist of at least one of the first and second chemoattractant receptors; and determining whether an identified antagonist is an antagonist for one of the first chemoattractant receptors, the second chemoattractant receptor, or both.

29. The method of claim 28, wherein the step of contacting the first and the second cell populations with a candidate antagonist, comprises contacting the first and the second cell populations with at least two candidate antagonists.

30. The method of claim 28, wherein the candidate antagonist is a **peptide**, **peptide**-like molecule, non-peptidyl organic compound, inorganic compound, nucleic acid or antibody.

31. The method of claim 28, wherein the inhibitory concentration of the ligand for the first chemoattractant receptor inhibits cell migration greater than or equal to about 50% of maximal ligand-activated cell migration.

32. The method of claim 28, wherein the inhibitory concentration of the ligand for the first chemoattractant receptor inhibits cell migration greater than or equal to about 95% of maximal ligand-activated cell migration.

33. The method of claim 28, wherein the inhibitory concentration of the ligand for the first chemoattractant receptor inhibits cell migration greater than or equal to about 100% of maximal ligand-activated cell migration.

34. The method of claim 28, wherein the inhibitory concentration of the ligand for the second chemoattractant receptor inhibits cell migration greater than or equal to about 50% of maximal ligand-activated cell migration.

35. The method of claim 28, wherein the inhibitory concentration of the ligand for the second chemoattractant receptor inhibits cell migration greater than or equal to about 95% of maximal ligand-activated cell migration.

36. The method of claim 28, wherein the inhibitory concentration of the ligand for the second chemoattractant receptor inhibits cell migration greater than or equal to about 100% of maximal ligand-activated cell migration.

37. The method of claim 28, wherein the first and second chemoattractant receptors are each independently a **chemokine receptor**.

38. The method of claim 37, wherein the **chemokine receptor** is selected from the group consisting of CCR, CXCR, CX3CR, and XCR classes of **chemokine receptors**.

39. The method of claim 38, wherein the **chemokine receptors** are

CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR11, CX3CR1 or XCR1.

40. The method of claim 28, wherein the ligand for the first chemoattractant receptor is a chemokine.

41. The method of claim 40, wherein the chemokine is selected from the group consisting of CCR, CXCR, and CX3CR.

42. The method of claim 41, wherein the chemokine is IL-8, GCP-2, Gro α, Gro β, Gro γ, ENA-78, PBP, MIG, IP-10, I-TAC, SDF-1α, BLC, MIP-1α, MIP-1β, RANTES, HCC-1, HCC-2, HCC-3, HCC-4, MCP-1, MCP-2, MCP-3, MCP-4, eotaxin-1, eotaxin-2, TARC, MDC, MIP-3α, MIP-3β, 6Ckine, I-309, TECK, lymphotactin, fractalkine, TCA-4, Exodus-2, Exodus-3, or CKβ-11.

43. The method of claim 28, wherein the ligand for the second chemoattractant receptor is a chemokine.

44. The method of claim 43, wherein the chemokine is selected from the group consisting of CCR, CXCR, and CX3CR.

45. The method of claim 44, wherein the chemokine is IL-8, GCP-2, Gro α, Gro β, Gro γ, ENA-78, PBP, MIG, IP-10, I-TAC, SDF-1α, BLC, MIP-1β, MIP-1, RANTES, HCC-1, HCC-2, HCC-3, HCC-4, MCP-1, MCP-2, MCP-3, MCP-4, eotaxin-1, eotaxin-2, TARC, MDC, MIP-3α, MIP-3β, 6Ckine, 1-309, TECK, lymphotactin, fractalkine, TCA-4, Exodus-2, Exodus-3, or CKβ-11.

46. The method of claim 28, wherein the ligands for the first and the second chemoattractant receptor are added simultaneously.

47. The method of claim 28, wherein the ligands for the first and the second chemoattractant receptor are added in series.

48. The method of claim 28, wherein the at least one candidate antagonist is contacted before the at least one of the ligands.

49. The method of claim 28, wherein the assaying migration comprises measuring a signal.

50. The method of claim 49, wherein the signal is a fluorescent signal.

51. The method of claim 28, wherein assaying migration comprises counting cells using a microscope.

52. The method of claim 28, wherein assaying comprises labeling cells with a marker.

53. The method of claim 52, wherein the marker is a dye or a radioactive label.

54. The method of claim 28, wherein determining is performed by a method comprising steps of: incubating a first cell population comprising first chemoattractant receptor with a candidate antagonist; incubating a second cell population comprising second chemoattractant receptor with the candidate antagonist; contacting the first cell population with an inhibitory concentration of a ligand for the first chemoattractant receptor; contacting the second cell population with an inhibitory concentration of a ligand for the second chemoattractant receptor; and assaying cell migration of the first and the second cell population, wherein cell migration identifies the candidate antagonist as an antagonist of either the first or the second chemoattractant receptor.

55. A kit comprising a cell migration apparatus, and at least one

chemokine.

56. The kit of claim 55, wherein the chemokine is lyophilized.

57. The kit of claim 55, wherein the kit comprises at least two chemokines.

58. The kit of claim 55, wherein the kit comprises at least three chemokines.

59. The kit of claim 55, wherein the at least one chemokine is in solution.

60. The kit of claim 55, further comprising a cell population comprising at least one **chemokine receptor**.

L10 ANSWER 8 OF 60 USPATFULL on STN
2003:325221 Chemokine variants and methods of use.
Oravecz, Tamas, Palo Alto, CA, UNITED STATES
Norcross, Michael A., Bethesda, MD, UNITED STATES
US 2003229203 A1 20031211
APPLICATION: US 2003-392355 A1 20030318 (10)
PRIORITY: US 1997-67033P 19971201 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides the nucleotide and amino acid sequence of truncated RANTES (3-68), which has the same amino acid sequence as the wild-type RANTES, but with a Serine/Proline truncation at positions 1 and 2 from the N-terminus, respectively. CD26 is a leukocyte activation marker that possesses dipeptidyl peptidase IV (DPPIV) activity but whose natural substrates and immunological functions had not been previously defined. Several chemokines, including RANTES (regulated on activation, normal T expressed and secreted) are provided, which are substrates for human CD26. The truncated RANTES (3-68) lacked the ability of native RANTES (1-68) to increase the cytosolic calcium concentration in human monocytes, but it still induces this response in macrophages activated with macrophage colony-stimulating factor (M-CSF). RANTES (3-68) retains the ability to stimulate **CCR5** receptors and to inhibit the cytopathic effects of HIV-1. The invention provides methods for identifying compounds that affect DPPIV-medicated chemokine cleavage, methods for inhibiting HIV infection and treating individuals having or at risk of having HIV infection, methods for diagnosis and/or prognosis of individuals having a chemokine-associated disorder and methods for accelerating wound healing and angiogenesis, all based on the discovery of DPPIV-mediated cleavage of chemokines.

CLM What is claimed is:

1. A substantially pure **polypeptide** having an amino acid sequence as set forth in SEQ ID NO:2.

2. An isolated polynucleotide which encodes an amino acid sequence as set forth in SEQ ID NO:2.

3. An isolated polynucleotide selected from the group consisting of: a) SEQ ID NO:1; b) SEQ ID NO:1, wherein T can also be U; c) nucleic sequences complementary to SEQ ID NO:1; d) fragments of a), b), or c) that are at least 15 bases in length and that will hybridize to DNA which encodes SEQ ID NO:2.

4. An expression vector containing in operable linkage the polynucleotide as in claim 2.

5. A host cell containing the vector of claim 4.

6. The host cell of claim 5, wherein the cell is a eukaryotic cell.

7. A method for identifying a compound which modulates dipeptidyl peptidase IV (DPPIV)-mediated chemokine processing comprising: a) incubating components comprising the compound, DPPIV and a chemokine under conditions sufficient to allow the components to interact; and b) determining the N-terminal amino acid sequence of the chemokine before and after incubating in the presence of the compound.

8. The method of claim 7, wherein the modulating is inhibition of DPPIV-mediated chemokine processing.

9. The method of claim 7, whererin the modulating is stimulation of DPPIV-mediated chemokine processing.

10. The method of claim 7, wherein the compound is a **peptide**.

11. The method of claim 7, wherein the compound is a peptidomimetic.

12. The method of claim 7, wherein the DPPIV is expressed in a cell.

13. The method of claim 7, wherein the chemokine contains a proline or an alanine at position 2 from the N-terminus.

14. A method of inhibiting membrane fusion between HIV and a target cell or between an HIV-infected cell and a CD4 positive uninfected cell comprising contacting the target or CD4 positive cell with a fusion-inhibiting effective amount of the **polypeptide** of SEQ ID NO:2.

15. The method of claim 14, wherein the contacting is by in vivo administration to a subject.

16. The method of claim 14, wherein the **polypeptide** is administered by intravenous, intramuscular or subcutaneous injection.

17. The method of claim 14, wherein the **polypeptide** is formulated in a pharmaceutically acceptable carrier.

18. A method of treating a subject having or at risk of having an HIV infection or disorder, comprising administering to the subject, a therapeutically effective amount of a **polypeptide** of SEQ ID NO:2, wherein the **polypeptide** inhibits cell-cell fusion in cells infected with HIV.

19. The method of claim 18, wherein the subject is suffering from AIDS or ARC.

20. The method of claim 18, wherein the **polypeptide** is formulated in a pharmaceutically acceptable carrier.

21. A method of treating a subject having an HIV-related disorder associated with expression of **CCR5** comprising administering to an HIV infected or susceptible cell of the subject, a **polypeptide** of SEQ ID NO:2 or a nucleic acid sequence encoding the **polypeptide** of SEQ ID NO:2 or other variant chemokine.

22. The method of claim 21, wherein the **polypeptide** or nucleic acid is introduced into the cell using a carrier.

23. The method of claim 22, wherein the carrier is a vector.

24. The method of claim 21, wherein the administering is ex vivo.

25. The method of claim 21, wherein the administering is in vivo.

26. A pharmaceutical composition comprising the **polypeptide** of SEQ ID NO:2 in a pharmaceutically acceptable carrier.

27. A pharmaceutical composition comprising CD26 **polypeptide** in a pharmaceutically acceptable carrier.

28. A method for producing a variant chemokine having an activity different from the activity of the wild-type chemokine, comprising contacting the wild-type chemokine with an N-terminal processing effective amount of Dipeptidyl peptidase IV (DPPIV), thereby truncating the chemokine and producing a variant chemokine.

29. The method of claim 28, wherein the chemokine contains a proline or an alanine at position 2 from the N-terminus.

30. The method of claim 29, wherein the chemokine is selected from the group consisting of RANTES, MIP-1, IP-10, cotaxin, MDC and MCP-2.

31. The method of claim 29, wherein the chemokine is RANTES.

32. A method for inhibiting HIV-1 replication in a host cell susceptible to HIV-1 infection, comprising contacting the cell or the host with an effective amount of Dipeptidyl peptidase IV (DPPIV) enzyme such that macrophage-derived chemokine (MDC) is cleaved to produce truncated MDC, thereby providing antiviral activity and inhibiting HIV-1 replication.

33. A method for inhibiting Dipeptidyl peptidase IV (DPPIV)-mediated chemokine processing comprising contacting DPPIV with an inhibiting effective amount of a compound which inhibits DPPIV expression or activity.

34. A method for inhibiting an allergic or inflammatory reaction in a subject, comprising administering to the subject an effective amount of Dipeptidyl peptidase IV (DPPIV) enzyme such that a chemokine is cleaved to produce a truncated chemokine, thereby inhibiting an allergic or inflammatory reaction.

35. The method of claim 34, wherein the chemokine is eotaxin.

36. The method of claim 34, wherein the subject is a human.

37. A method for accelerating angiogenesis or wound healing in a subject, comprising administering to the subject an effective amount of an inhibitor of Dipeptidyl peptidase IV (DPPIV) enzyme activity or gene expression or a DPPIV-insensitive chemokine, such that chemokine processing is inhibited, thereby accelerating angiogenesis or wound healing.

38. The method of claim 37, wherein the chemokine is IP-10.

39. The method of claim 37, wherein the DPPIV-insensitive chemokine is a wild-type chemokine with the proviso that alanine or proline at position 2 is replaced with any amino acid other than alanine or proline.

40. A method for inhibiting HIV-1 replication in a host cell susceptible to HIV-1 infection, comprising contacting the cell or the host with an effective amount of Dipeptidyl peptidase IV (DPPIV) enzyme such that RANTES is cleaved to produce truncated RANTES, thereby providing antiviral activity and inhibiting HIV-1 replication.

41. The method as in any of claims 7, 28, 32, 33, 34, 37, or 39, wherein the DPPIV enzyme is CD26.

42. A method of diagnosis of a subject having a chemokine-associated disorder comprising: identifying the presence of a chemokine of interest from a specimen isolated from the subject; determining the amino-terminal sequence of the chemokine, wherein a full-length amino acid sequence is indicative of the presence of a wild-type chemokine **polypeptide** and a truncated amino-terminal sequence is indicative of

the presence of a variant chemokine, and determining the concentration of wild-type chemokine as compared to variant chemokine, thereby providing a diagnosis of the subject.

43. The method of claim 42, wherein the determining of the amino-terminal sequence of the chemokine is by contacting the chemokine with an antibody which distinguishes wild-type from variant chemokine **polypeptide**.

44. The method of claim 42, wherein the specimen is selected from the group consisting of blood, sputum, urine, saliva, cerebrospinal fluid, and serum.

45. Antibodies which bind to wild-type chemokine but not to DPPIV-truncated chemokine.

46. Antibodies which bind to DPPIV-truncated chemokine but not to wild-type chemokine.

47. The antibodies as in claims 45 or 46, wherein the chemokine is RANTES.

L10 ANSWER 9 OF 60 USPATFULL on STN
2003:324332 Anti-**CCR5** antibody.
Olson, William C., Ossining, NY, UNITED STATES
Maddon, Paul J., Scarsdale, NY, UNITED STATES
Tsurushita, Naoya, Palo Alto, CA, UNITED STATES
Hinton, Paul R., Sunnyvale, CA, UNITED STATES
Vasquez, Maximiliano, Palo Alto, CA, UNITED STATES
US 2003228306 A1 20031211
APPLICATION: US 2003-371483 A1 20030221 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention is directed an anti-**CCR5** antibody which comprises (i) two light chains, each light chain comprising the expression product of a plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising an expression product of either a plasmid designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or a plasmid designated pVg1:HuPRO140 (mutB+D+I)-VH (ATCC Deposit Designation PTA-4099) or a fragment thereof which binds to **CCR5** on the surface of a human cell.
CLM What is claimed is:
1. An anti-**CCR5** antibody which comprises (i) two light chains, each light chain comprising the expression product of a plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the expression product of either a plasmid designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or a plasmid designated pVg1:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099), or a fragment of such antibody, which binds to **CCR5** on the surface of a human cell.

2. The anti-**CCR5** antibody of claim 1, wherein the heavy chains are expressed by the plasmid designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098).

3. The anti-**CCR5** antibody of claim 1, wherein the heavy chains are expressed by the plasmid designated pVg1:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099).

4. An anti-**CCR5** antibody comprising two light chains, each chain comprising consecutive amino acids, the amino acid sequence of which is set forth in SEQ ID NO: 6, and two heavy chains, each heavy chain comprising consecutive amino acids, the amino acid sequence of which is set forth in SEQ ID NO: 9.

5. An anti **CCR5** antibody comprising two light chains, each light chain comprising consecutive amino acids, the amino acid sequence of which is set forth in SEQ ID NO: 6, and two heavy chains, each heavy chain comprising consecutive amino acids, the amino acid sequence of which is set forth in SEQ ID NO: 12.

6. An isolated nucleic acid encoding a **polypeptide** comprising consecutive amino acids, the amino acid sequence of which is set forth in SEQ ID NO: 6.

7. The nucleic acid of claim 6, wherein the consecutive amino acids are the amino acids expressed by a plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097).

8. The nucleic acid of claim 6, wherein the nucleic acid comprises the sequence set forth in SEQ ID NO: 5.

9. The nucleic acid of any one of claims 6, 7 or 8, wherein the nucleic acid is RNA, DNA or cDNA.

10. An isolated nucleic acid encoding a **polypeptide** comprising consecutive amino acids, the amino acid sequence of which is set forth in SEQ ID NO: 9.

11. The nucleic acid of claim 10, wherein the consecutive amino acids are the amino acids expressed by a plasmid designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098).

12. The nucleic acid of claim 10, wherein the nucleic acid comprises the sequence set forth in SEQ ID NO: 8.

13. The nucleic acid of any one of claims 10, 11 or 12 wherein the nucleic acid is RNA, DNA or cDNA.

14. An isolated nucleic acid encoding a **polypeptide** comprising consecutive amino acids, the amino acid sequence of which is set forth in SEQ ID NO: 12.

15. The nucleic acid of claim 14, wherein the consecutive amino acids are the amino acids expressed by a plasmid designated pVg1:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099)

16. The nucleic acid of claim 14, wherein the nucleic acid comprises the sequence set forth in SEQ ID NO: 11.

17. The nucleic acid of any one of claims 14, 15 and 16, wherein the nucleic acid is RNA, DNA or cDNA.

18. A composition comprising at least one of the anti-**CCR5** antibody or a fragment thereof, of any one of claims 1-5 and a carrier.

19. A composition comprising the anti-**CCR5** antibody or a fragment thereof, of any one of claims 1-5, having attached thereto a material selected from the group consisting of a radioisotope, a toxin, polyethylene glycol, a cytotoxic agent and a detectable label.

20. A method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with an antibody which comprises (i) two light chains, each light chain comprising the expression product of a plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the expression product of either a plasmid designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or a plasmid designated pVg1:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099), or a fragment of such antibody which binds to **CCR5** on the surface of the CD4+ cell, in an amount and under conditions such that fusion of HIV-1

of an HIV-1 infected cell to the CD4+ cell is inhibited, thereby inhibiting HIV-1 infection of the CD4+ cell.

21. The method of claim 20, wherein the CD4+ cell expresses **CCR5**.

22. A method of treating a subject afflicted with HIV-1 which comprises administering to the subject an effective HIV-1 treating dosage amount of an anti-**CCR5** antibody comprising (i) two light chains, each light chain comprising the expression product of a plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the expression product of either a plasmid designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or a plasmid designated pVg1:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099), or a fragment of such antibody, which binds to **CCR5** on the surface of a human cell, under conditions effective to treat said HIV-1-afflicted subject.

23. A method of preventing a subject from contracting an HIV-1 infection which comprises administering to the subject an effective HIV-1 infection-preventing dosage amount of an anti-**CCR5** antibody comprising (i) two light chains, each light chain comprising the expression product of a plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the expression product of either a plasmid designated pVg1:HuPRO 140 HG2-VH (ATCC Deposit Designation PTA-4098) or a plasmid designated pVg1:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099), or a fragment of such antibody, which binds to **CCR5** on the surface of a human cell, under conditions effective to prevent said HIV-1 infection in said subject.

24. The method of claim 22 or 23, wherein the anti-**CCR5** antibody is administered to the subject by a method selected from the group consisting of intravenous, intramuscular and subcutaneous means.

25. The method of claim 22 or 23, wherein the anti-**CCR5** antibody is administered continuously to said subject.

26. The method of claim 22 or 23 wherein the anti-**CCR5** antibody is administered at predetermined periodic intervals to said subject.

27. The method of claim 22 or 23, which further comprises labeling the anti-**CCR5** antibody with a detectable marker.

28. The method of claim 27, wherein the detectable marker is a radioactive or a fluorescent marker.

29. The method of claim 22 or 23, wherein the dosage of said anti-**CCR5** antibody ranges from about 0.1 to about 100,000 μg/kg body weight of said subject.

30. The method of claim 29, wherein the dosage of said anti-**CCR5** antibody does not inhibit an endogenous chemokine activity on **CCR5** in said subject.

31. An anti-**CCR5** antibody conjugate comprising an anti-**CCR5** antibody which comprises (i) two light chains, each light chain comprising the expression product of a plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the expression product of either a plasmid designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or a plasmid designated pVg1:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099), or a fragment of such antibody which binds to **CCR5** on the surface of a human cell, conjugated to at least one polymer.

32. The anti-**CCR5** antibody conjugate of claim 31, wherein the polymer is selected from the group consisting of hydrophilic polyvinyl polymers,

polyalkylene ethers, polyoxyalkylenes, polymethacrylates, carbomers, branched polysaccharides, unbranched polysaccharides, polymers of sugar alcohols, heparin and heparon.

33. The anti-**CCR5** antibody conjugate of claim 32, wherein the polyalkylene ether is polyethylene glycol (PEG) or a derivative thereof.

34. The anti-**CCR5** antibody conjugate of claim 33, wherein at least one PEG has an average molecular weight of at least 20 kD.

35. The anti-**CCR5** antibody conjugate of claim 31, wherein the apparent size of the conjugate is at least about 500 kD.

36. The anti-**CCR5** antibody conjugate of claim 31, wherein the conjugate has at least one of an increase in serum half-life, an increase in mean residence time in the circulation and a decrease in serum clearance rate, compared to a nonconjugated anti-**CCR5** antibody or fragment thereof.

37. A method of inhibiting infection of a **CCR5**+ cell by HIV-1, which method comprises administering to a subject at risk of HIV-1 infection the conjugate of claim 31 in an amount and under conditions effective to inhibit infection of **CCR5**+ cells of said subject by HIV-1.

38. A method of treating an HIV-1 infection in a subject, which method comprises administering to an HIV-1-infected subject the conjugate of claim 31 in an amount and under conditions effective to treat the subject's HIV-1 infection.

39. The method of claim 38, wherein the amount of the conjugate is effective in reducing a viral load in the subject.

40. The method of claim 38, wherein the amount of the conjugate is effective in increasing a CD4+ cell count in the subject.

41. The method of claim 38, which further comprises administering to said subject at least one conventional anti-viral agent.

42. The method of claim 37 or 38, wherein the conjugate is administered to the subject by a method selected from the group consisting of intravenous, intramuscular and subcutaneous means.

43. The method of claim 37 or 38, wherein the conjugate is administered continuously to said subject.

44. The method of claim 37 or 38, wherein the conjugate is administered at predetermined periodic intervals to said subject.

45. The method of claim 37 or 38, which further comprises labeling the conjugate with a detectable marker.

46. The method of claim 45, wherein the detectable marker is a radioactive or a fluorescent marker.

47. A transformed host cell comprising at least two vectors, at least one vector comprising a nucleic acid sequence encoding heavy chains of an anti-**CCR5** antibody, and at least one vector comprising a nucleic acid sequence encoding light chains of the anti-**CCR5** antibody, wherein the anti-**CCR5** antibody comprises two heavy chains having the amino acid sequence set forth in SEQ ID NO: 9, and two light chains having the amino acid sequence set forth in SEQ ID NO: 6.

48. A transformed host cell comprising at least two vectors, at least one vector comprising a nucleic acid sequence encoding heavy chains of an anti-**CCR5** antibody, and at least one vector comprising a nucleic acid sequence encoding light chains of the anti-**CCR5** antibody, wherein

the anti-**CCR5** antibody comprises two heavy chains having the amino acid sequence set forth in SEQ ID NO: 12, and two light chains having the amino acid sequence set forth in SEQ ID NO: 6.

49. The transformed host cell of claim 47 or 48, wherein the cell is a mammalian cell.

50. The transformed host cell of claim 49 wherein the cell is a COS cell, a CHO cell or a myeloma cell.

51. The transformed host cell of claim 47 or 48, wherein the cell secretes the anti-**CCR5** antibody.

52. The transformed host cell of claim 47, wherein the vector encoding heavy chains is designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098).

53. The transformed host cell of claim 48, wherein the vector encoding heavy chains is designated pVg1:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099).

54. The transformed host cell of claim 47 or 48, wherein the vector encoding light chains is designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097).

55. The transformed host cell of claim 47, wherein the vector encoding heavy chains is designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) and the vector encoding light chains is designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097).

56. The transformed host cell of claim 48, wherein the vector encoding the heavy chains is designated pVg1:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099) and the vector encoding light chains is designated pVK-HuPRO140-VK (ATCC Deposit Designation PTA-4097).

57. The transformed host cell of claim 47, wherein the nucleic acid sequence encoding heavy chains has the nucleic acid sequence set forth in SEQ. ID NO: 8.

58. The transformed host cell of claim 48, wherein the nucleic acid sequence encoding heavy chains has the nucleic acid sequence set forth in SEQ ID NO: 11.

59. The transformed host cell of claim 47 or 48 wherein the nucleic acid sequence encoding light chains has the nucleic acid sequence set forth in SEQ ID NO: 5.

60. A vector comprising a nucleic acid sequence encoding a heavy chain of an anti-**CCR5** antibody, wherein the heavy chain comprises the amino acid sequence set forth in SEQ ID NO: 9.

61. The vector of claim 60, wherein the vector is designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation No. PTA-4098).

62. A vector comprising a nucleic acid sequence encoding a heavy chain of an anti-**CCR5** antibody, wherein the heavy chain comprises the amino acid sequence set forth in SEQ ID NO: 12.

63. The vector of claim 62, wherein the vector is designated pVg1:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation No. PTA-4099).

64. A vector comprising a nucleic acid sequence encoding a light chain of an anti-**CCR5** antibody, wherein the light chain comprises the amino acid sequence set forth in SEQ ID NO: 6.

65. The vector of claim 64, wherein the vector is designated

pVK:HuPRO140-VK (ATCC Deposit Designation NO: PTA-4097).

66. A process for producing an anti-**CCR5** antibody which comprises culturing a host cell containing therein (i) a plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) either a plasmid designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or a plasmid designated pVg1:PRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099) under conditions permitting the production of an antibody comprising two light chains encoded by the plasmid designated pVK:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4097)and two heavy chains encoded either by the plasmid designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg1:HuPRO 140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099), so as to thereby produce an anti-**CCR5** antibody.

67. A process for producing an anti-**CCR5** antibody which comprises: a) transforming a host cell with (i) a plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) either a plasmid designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or a plasmid designated pVg1:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099); and b) culturing the transformed host cell under conditions permitting production of an antibody comprising two light chains encoded by the plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097) and two heavy chains encoded either by the plasmid designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg1:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099), so as to thereby produce an anti-**CCR5** antibody.

68. The method of claim 66 or 67, which further comprises recovering the anti-**CCR5** antibody so produced in isolated form.

69. The method of claim 66 or 67, wherein the host cell is a mammalian cell.

70. The method of claim 69, wherein the mammalian host cell is a COS cell, a CHO cell or a myeloma cell.

71. The method of claim 66 or 67, wherein the heavy chains of the anti-**CCR5** antibody are encoded by the plasmid designated pVg1:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098).

72. The method of claim 66 or 67, wherein the heavy chains of the anti-**CCR5** antibody are encoded by the plasmid designated pVg1:HuPRO140 (mut B+D+I) (ATCC Deposit Designation PTA-4099).

73. A kit for use in a process of producing an anti-**CCR5** antibody comprising: a) a vector comprising a nucleic acid sequence encoding a light chain of an anti-**CCR5** antibody, wherein the light chain comprises the amino acid sequence set forth in SEQ ID NO: 6; and b) a vector comprising a nucleic acid sequence encoding a heavy chain of an anti-**CCR5** antibody, wherein the heavy chain comprises the amino acid sequence set forth in SEQ ID NO: 9, or a vector comprising a nucleic acid sequence encoding a heavy chain of an anti-**CCR5** antibody, wherein the heavy chain comprises the amino acid sequence set forth in SEQ ID NO: 12.

L10 ANSWER 14 OF 60 USPATFULL on STN
2003:277321 CC **chemokine receptor** 5 DNA, new animal models and therapeutic agents for HIV infection.
Combadiere, Christophe, Rockville, MD, UNITED STATES
Feng, Yu, San Diego, CA, UNITED STATES
Alkhatib, Ghalib, Bethesda, MD, UNITED STATES
Berger, Edward A., Rockville, MD, UNITED STATES
Murphy, Philip M., Rockville, MD, UNITED STATES
Broder, Christopher C., Rockville, MD, UNITED STATES

Kennedy, Paul E., Silver Spring, MD, UNITED STATES
The United States of America, represented by the Secretary, (U.S. corporation)Department of Health and Human Services (U.S. corporation)
US 2003195348 A1 20031016
APPLICATION: US 2003-439845 A1 20030515 (10)
PRIORITY: US 1996-18508P 19960528 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The susceptibility of human macrophages to human immunodeficiency virus (HIV) infection depends on cell surface expression of the human CD4 molecule and CC cytokine receptor 5. **CCR5** is a member of the 7-transmembrane segment superfamily of G-protein-coupled cell surface molecules. **CCR5** plays an essential role in the membrane fusion step of infection by some HIV isolates. The establishment of stable, nonhuman cell lines and transgenic mammals having cells that coexpress human CD4 and **CCR5** provides valuable tools for the continuing research of HIV infection. In addition, antibodies which bind to **CCR5**, **CCR5** variants, and **CCR5**-binding agents, capable of blocking membrane fusion between HIV and target cells represent potential anti-HIV therapeutics for macrophage-tropic strains of HIV.
CLM What is claimed is:
1. An isolated polynucleotide which encodes an amino acid sequence as set forth in SEQ ID NO:2 or SEQ ID NO:4.

2. An isolated polynucleotide selected from the group consisting of: a) SEQ ID NO:1; b) SEQ ID NO:3; c) SEQ ID NO:1, wherein T can also be U; d) SEQ ID NO:3, wherein T can also be U; e) nucleic sequences complementary to SEQ ID NO:1; f) nucleic sequences complementary to SEQ ID NO:3; g) fragments of a), c), or e) that are at least 15 bases in length and that will selectively hybridize to genomic DNA which encodes the **CCR5** protein of SEQ ID NO:2; and h) fragments of b), d), or f) that are at least 15 bases in length and that will selectively hybridize to genomic DNA which encodes the **CCR5** protein of SEQ ID NO:4.

3. The polynucleotide of claim 2, wherein the polynucleotide fragments encode a **peptide** selected from the group consisting of AAQWDFGNTMC (SEQ ID NO:4), RSQKEGLHYTCSSHFPYSQYQFWK (SEQ ID NO:5), and QEFFGLNNCSSSNRLD (SEQ ID NO:6).

4. An expression vector containing in operable linkage the polynucleotide as in claim 1.

5. A host cell containing the vector of claim 4.

L10 ANSWER 22 OF 60 USPATFULL on STN
2003:201584 Sulfated **CCR5** peptides for HIV-1 infection.
Dragic, Tatjana, Scarsdale, NY, UNITED STATES
Olson, William C., Ossining, NY, UNITED STATES
Progenics Pharmaceuticals, Inc. (U.S. corporation)
US 2003139571 A1 20030724
APPLICATION: US 2002-323314 A1 20021219 (10)
PRIORITY: US 2001-267231P 20010207 (60)
US 2000-205839P 20000519 (60)
US 2000-185667P 20000229 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a compound comprising the structure: θαYDINYYTSEβλ wherein each T represents a threonine, each S represents a serine, each E represents a glutamic acid, each Y represents a tyrosine; each D represents an aspartic acid, each I represents an isoleucine; and each N represents an asparagine; wherein α represents from 0 to 9 amino acids, with the proviso that if there are more than 2 amino acids, they are joined by peptide bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the I at position 9 and

extending therefrom in the amino terminal direction; wherein p represents from 0 to 13 amino acids, with the proviso that if there are more than 2 amino acids, they are joined by peptide bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the P at position 19 and extending therefrom in the carboxy terminal direction; wherein θ represents an amino group or an acetylated amino group; wherein λ represents a carboxyl group or an amidated carboxyl group; wherein all of α,Y,D,I,N,Y,Y,T,S,E and β are joined together by peptide bonds; further provided that at least two tyrosines in the compound are sulfated.

CLM What is claimed is:

1. A compound comprising the structure: θαYDINYYTSEβ.la mbda. wherein each T represents a threonine, each S represents a serine, each E represents a glutamic acid, each Y represents a tyrosine; each D represents an aspartic acid, each I represents an isoleucine; and each N represents an asparagine; wherein α represents from 0 to 9 amino acids, with the proviso that if there are more than 2 amino acids, they are joined by **peptide** bonds in consecutive order and have a sequence identical to the sequence-set forth in SEQ ID NO: 1 beginning with the I at position 9 and extending therefrom in the amino terminal direction; wherein β represents from 0 to 13 amino acids, with the proviso that if there are more than 2 amino acids, they are joined by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the P at position 19 and extending therefrom in the carboxy terminal direction; wherein θ represents an amino group or an acetylated amino group; wherein λ represents a carboxyl group or an amidated carboxyl group; wherein all of α,Y,D,I,N,Y,Y,T,S,E and β are joined together by **peptide** bonds; further provided that at least two tyrosines in the compound are sulfated.

2. The compound of claim 1, wherein β represents less than 17 amino acids.

3. The compound of claim 1, wherein β represents less than 16 amino acids.

4. The compound of claim 1, wherein β represents less than 15 amino acids.

5. The compound of claim 1, wherein β represents less than 14 amino acids.

6. The compound of claim 1, wherein β represents less than 13 amino acids.

7. The compound of claim 1, wherein β represents less than 12 amino acids.

8. The compound of claim 1, wherein β represents less than 11 amino acids.

9. The compound of claim 1, wherein β represents less than 10 amino acids.

10. The compound of claim 1, wherein β represents less than 9 amino acids.

11. The compound of claim 1, wherein β represents less than 8 amino acids.

12. The compound of claim 1, wherein β represents less than 7 amino acids.

13. The compound of claim 1, wherein β represents less than 6 amino acids.

14. The compound of claim 1, wherein β represents less than 5 amino acids.

15. The compound of claim 1, wherein β represents less than 4 amino acids.

16. The compound of claim 1, wherein β represents less than 3 amino acids.

17. The compound of claim 1, wherein β represents less than 2 amino acids.

18. The compound of claim 1, wherein β represents less than 1 amino acid.

19. The compound of claim 1, wherein α represents less than 9 amino acids.

20. The compound of claim 1, wherein α represents less than 8 amino acids.

21. The compound of claim 1, wherein α represents less than 7 amino acids.

22. The compound of claim 1, wherein α represents less than 6 amino acids.

23. The compound of claim 1, wherein α represents less than 5 amino acids.

24. The compound of claim 1, wherein α represents less than 4 amino acids.

25. The compound of claim 1, wherein α represents less than 3 amino acids.

26. The compound of claim 1, wherein α represents less than 2 amino acids.

27. The compound of claim 1, wherein α represents less than 1 amino acid.

28. A composition comprising the compound of claim 1 and a detectable marker attached thereto.

29. The composition of claim 28, wherein the detectable marker is biotin.

30. The composition of claim 28, wherein the detectable marker is attached at the C-terminus of the compound.

31. A composition which comprises a carrier and an amount of the compound of claim 1 effective to inhibit binding of HIV-1 to a **CCR5** receptor on the surface of a CD4+ cell.

32. A method of inhibiting human immunodeficiency virus infection of a CD4+ cell which also carries a **CCR5** receptor on its surface which comprises contacting the CD4+ cell with an amount of the compound of claim 1 effective to inhibit binding of human immunodeficiency virus to the **CCR5** receptor so as to thereby inhibit human immunodeficiency

virus infection of the CD4+ cell.

33. The method of claim 32, wherein the CD4+ cell is present in a subject and the contacting is effected by administering the compound to the subject.

34. A method of preventing CD4+ cells of a subject from becoming infected with human immunodeficiency virus which comprises administering to the subject an amount of the compound of claim 1 effective to inhibit binding of human immunodeficiency virus to **CCR5** receptors on the surface of the CD4+ cells so as to thereby prevent the subject's CD4+ cells from becoming infected with human immunodeficiency virus.

35. A method of treating a subject whose CD4+ cells are infected with human immunodeficiency virus which comprises administering to the subject an amount of the compound of claim 1 effective to inhibit binding of human immunodeficiency virus to **CCR5** receptors on the surface of the subject's CD4+ cells so as to thereby treat the subject.

36. The method of any one of claims 33-35, wherein the compound is administered by aerosol, intravenous, oral or topical route.

37. The method of claim 33 or 35, wherein the subject is infected with HIV-1 prior to administering the compound to the subject.

38. The method of claim 33 or 34, wherein the subject is not infected with HIV-1 prior to administering the compound to the subject.

39. The method of claim 38, wherein the subject is not infected with, but has been exposed to, human immunodeficiency virus.

40. The method of any one of claims 33-35, wherein the effective amount of the compound comprises from about 1.0 ng/kg to about 100 mg/kg body weight of the subject.

41. The method of claim 40, wherein the effective amount of the compound comprises from about 100 ng/kg to about 50 mg/kg body weight of the subject.

42. The method of claim 41, wherein the effective amount of the compound comprises from about 1 μg/kg to about 10 mg/kg body weight of the subject.

43. The method of claim 42, wherein the effective amount of the compound comprises from about 100 μg/kg to about 1 mg/kg body weight of the subject.

44. The method of any one of claims 33-35, wherein the subject is a human being.

45. A method of identifying an agent which inhibits binding of a **CCR5** ligand to a **CCR5** receptor which comprises: (a) immobilizing the compound of claim 1 on a solid support; (b) contacting the immobilized compound from step (a) with sufficient detectable **CCR5** ligand to saturate all binding sites for the **CCR5** ligand on the immobilized compound under conditions permitting binding of the **CCR5** ligand to the immobilized compound so as to form a complex; (c) removing any unbound **CCR5** ligand; (d) contacting the complex from step (b) with the agent; and (e) detecting whether any **CCR5** ligand is displaced from the complex, wherein displacement of detectable **CCR5** ligand from the complex indicates that the agent binds to the compound so as to thereby identify the agent as one which inhibits binding of the **CCR5** ligand to the **CCR5** receptor.

46. A method of identifying an agent which inhibits binding of a **CCR5** ligand to a **CCR5** receptor which comprises: (a) contacting the

compound of claim 1 with sufficient detectable **CCR5** ligand to saturate all binding sites for the **CCR5** ligand on the compound under conditions permitting binding of the **CCR5** ligand to the compound so as to form a complex; (b) removing any unbound **CCR5** ligand; (c) measuring the amount of **CCR5** ligand which is bound to the compound in the complex; (d) contacting the complex from step (a) with the agent so as to displace **CCR5** ligand from the complex; (e) measuring the amount of **CCR5** ligand which is bound to the compound in the presence of the agent; and (f) comparing the amount of **CCR5** ligand bound to the compound in step (e) with the amount measured in step (c), wherein a reduced amount measured in step (e) indicates that the agent binds to the compound so as to thereby identify the agent as one which inhibits binding of the **CCR5** ligand to the **CCR5** receptor.

47. A method of identifying an agent which inhibits binding of a **CCR5** ligand to a **CCR5** receptor which comprises: (a) immobilizing the compound of claim 1 on a solid support; (b) contacting the immobilized compound from step (a) with the agent and detectable **CCR5** ligand under conditions permitting binding of the **CCR5** ligand to the immobilized compound so as to form a complex; (c) removing any unbound **CCR5** ligand; (d) measuring the amount of detectable **CCR5** ligand which is bound to the immobilized compound in the complex; (e) measuring the amount of detectable **CCR5** ligand which binds to the immobilized compound in the absence of the agent; (f) comparing the amount of **CCR5** ligand which is bound to the immobilized compound in step (e) with the amount measured in step (d), wherein a reduced amount measured in step (d) indicates that the agent binds to the compound or **CCR5** ligand so as to thereby identify the agent as one which inhibits binding of the **CCR5** ligand to the **CCR5** receptor.

48. The method of claim 47, wherein the amount of the detectable ligand in step (a) and step (e) is sufficient to saturate all binding sites for the **CCR5** ligand on the compound.

49. A method of identifying an agent which inhibits binding of a **CCR5** ligand to a **CCR5** receptor which comprises: (a) contacting the compound of claim 1 with the agent and detectable **CCR5** ligand under conditions permitting binding of the **CCR5** ligand to the compound so as to form a complex; (b) removing any unbound **CCR5** ligand; (c) measuring the amount of detectable **CCR5** ligand which is bound to the compound in the complex; (d) measuring the amount of detectable **CCR5** ligand which binds to the compound in the absence of the agent; (e) comparing the amount of **CCR5** ligand which is bound to the compound in step (c) with the amount measured in step (d), wherein a reduced amount measured in step (c) indicates that the agent binds to the compound or **CCR5** ligand so as to thereby identify the agent as one which inhibits binding of the **CCR5** ligand to the **CCR5** receptor.

50. The method of claim 49, wherein the amount of the detectable ligand in step (a) and step (d) is sufficient to saturate all binding sites for the **CCR5** ligand on the compound.

51. The method of any one of claims 45-50, wherein the detectable **CCR5** ligand is labeled with a detectable marker.

52. A method of identifying an agent which inhibits binding of a **CCR5** ligand to a **CCR5** receptor which comprises: a) immobilizing the compound of claim 1 on a solid support; b) contacting the immobilized compound from step a) with the agent dissolved or suspended in a known vehicle and measuring the binding signal generated by such contact; c) contacting the immobilized compound from step a) with the known vehicle in the absence of the compound and measuring the binding signal generated by such contact; d) comparing the binding signal measured in step b) with the binding signal measured in step c), wherein an increased amount measured in step b) indicates that the agent binds to the compound so as to thereby identify the agent as one which binds to

the **CCR5** receptor.

53. The method of claim 52, wherein the solid support is a surface plasmon resonance sensor chip.

54. The method of claim 52 or 53, wherein the binding signal is measured by surface plasmon resonance.

55. A method of obtaining a composition which comprises: (a) identifying a compound which inhibits binding of a **CCR5** ligand to a **CCR5** receptor according to the method of any one of claims 45-50 and 52; and (b) admixing the compound so identified or a homolog or derivative thereof with a carrier.

56. The method of any one of claims 45-50 and 52, wherein the **CCR5** ligand is a complex comprising an HIV-1 envelope glycoprotein and a CD4-based protein.

57. The method of claim 56, wherein the HIV-1 envelope glycoprotein is gp120, gp140 or gp160.

58. The method of claim 56, wherein the CD4-based protein is soluble CD4 or CD4-IgG2.

59. The method of any one of claims 45-50 and 52, wherein the **CCR5** ligand is a chemokine.

60. The method of claim 59, wherein the chemokine is RANTES, MIP-1α or MIP-1β.

61. The method of any one of claims 45-50 and 52, wherein the **CCR5** ligand is an antibody.

62. The method of claim 61, wherein the antibody is selected from the group consisting of PA8 (ATCC Accession No. HB-12605), PA10 (ATCC Accession No.12607), PA11 (ATCC Accession No. HB-12608), PA12 (ATCC Accession No. HB-12609).

63. The method of claim 45 or 47, wherein the solid support is a microtiter plate well, a bead or surface plasmon resonance sensor chip.

64. A compound having the structure: Δ-$(\alpha YDINYYTSE\beta\lambda)_{\pi}$ wherein each T represents a threonine, each S represents a serine, each E represents a glutamic acid, each Y represents a tyrosine; each D represents an aspartic acid, each I represents an isoleucine; and each N represents an asparagine; wherein a represents from 0 to 9 amino acids, with the proviso that if there are more than 2 amino acids, they are joined together by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the I at position 9 and extending therefrom in the amino terminal direction; wherein β represents from 0 to 13 amino acids, with the proviso that if there are more than 2 amino acids, they are joined together by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the P at position 19 and extending therefrom in the carboxy terminal direction; wherein λ represents a carboxyl group or an amidated carboxyl group; wherein all of α,Y,D,I,N,Y,Y,T,S,E and β are joined together by **peptide** bonds, further provided that at least two tyrosines in the compound are sulfated, wherein π is an integer from 1 to 8, Δ is a polymer, and the solid line represents up to 8 linkers which attach the structure in parentheses to Δ.

65. A compound having the structure: (θαYDINYYTSEβ).sub .π-Δ wherein each T represents a threonine, each S represents a

serine, each E represents a glutamic acid, each Y represents a tyrosine, each D represents an aspartic acid, each I represents an isoleucine; and each N represents an asparagine; wherein α represents from 0 to 9 amino acids, with the proviso that if there are more than 2 amino acids, they are joined together by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the I at position 9 and extending therefrom in the amino terminal direction; wherein β represents from 0 to 13 amino acids, with the proviso that if there are more than 2 amino acids, they are joined together by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the P at position 19 and extending therefrom in the carboxy terminal direction; wherein θ represents an amino group or an acetylated amino group; wherein all of α,Y,D,I,N,Y,Y,T,S,E and β are joined together by **peptide** bonds, further provided that at least two tyrosines in the compound are sulfated, wherein π is an integer from 1 to 8, Δ is a polymer, and the solid line represents up to 8 linkers which attach the structure in parentheses to Δ.

66. The compound of claim 64 or 65, wherein the polymer is selected from the group consisting of a linear lysine polymer, a branched lysine polymer, a linear arginine polymer, a branched arginine polymer, polyethylene glycol, a linear acetylated lysine polymer, a branched acetylated lysine polymer, a linear chloroacetylated lysine polymer and a branched chloroacetylated lysine polymer.

67. The compound of claim 1, wherein the compound is a **peptide** which comprises consecutive amino acids having the sequence YDINYYTSE.

68. The compound of claim 67, wherein the tyrosines at positions 1 and 5 of the sequence YDINYYTSE are sulfated.

69. A compound comprising the structure: $\theta\alpha$YD$\pi\pi$Yπ.p
i.πE$\beta\lambda$ wherein each E represents a glutamic acid, and each Y represents a tyrosine; wherein α represents from 0 to 9 amino acids, with the proviso that if there are more than 2 amino acids, they are joined by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the I at position 9 and extending therefrom in the amino terminal direction; wherein β represents from 0 to 13 amino acids, with the proviso that if there are more than 2 amino acids, they are joined by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the P at position 19 and extending therefrom in the carboxy terminal direction; wherein θ represents an amino group or an acetylated amino group; wherein λ represents a carboxyl group or an amidated carboxyl group; wherein π represents any amino acid, wherein all of α,Y,D,π,π,Y,π,π,π,E and β are joined together by **peptide** bonds; further provided that at least two tyrosines in the compound are sulfated.

70. The compound of claim 69, wherein the compound is a **peptide** which comprises consecutive amino acids have the sequence YD$\pi\pi$Y$\pi\pi\pi$E.

71. The compound of claim 70, wherein the tyrosines at positions 1 and 5 of the sequence YD$\pi\pi$Y$\pi\pi\pi$E are sulfated.

72. A compound comprising the structure: $\theta\alpha$YDINYYTSEβ.l
ambda. wherein each T represents a threonine, each S represents a serine, each E represents a glutamic acid, each Y represents a tyrosine; each D represents an aspartic acid, each I represents an isoleucine; and each N represents an asparagine; wherein α represents from 0 to 9

amino acids, with the proviso that if there are more than 2 amino acids, they are joined by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the I at position 9 and extending therefrom in the amino terminal direction; wherein β represents from 0 to 13 amino acids, with the proviso that if there are more than 2 amino acids, they are joined by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the P at position 19 and extending therefrom in the carboxy terminal direction; wherein θ represents an amino group or an acetylated amino group; wherein λ represents a carboxyl group or an amidated carboxyl group; wherein all of α,Y,D,I,N,Y,Y,T,S,E and β are joined together by **peptide** bonds; further provided that at least two tyrosines in the compound are sulfated, wherein any amino acid except for the Y at position 1, D at position 2, Y at position 5 and E at position 9 may be replaced with a homologous amino acid.

73. The compound of claim 72, wherein any I amino acid residue is be replaced with a G,A,V or L amino acid residue.

74. The compound of claim 72, wherein any N amino acid residue is replaced with a Q amino acid residue.

75. The compound of claim 72, wherein any Y amino acid residue is replaced with an F or W amino acid residue.

76. The compound of claim 72, wherein any T amino acid residue is replaced with an S amino acid residue.

77. The compound of claim 72, wherein any S is replaced with a T amino acid residue.

78. The compound of claim 72, wherein any C is replaced with an M, S, T, A, GI N, or Q amino acid residue.

L10 ANSWER 27 OF 60 USPATFULL on STN
2003:134543 Sulfated **CCR5** peptides for HIV-1 infection.
Dragic, Tatjana, Scarsdale, NY, UNITED STATES
Olson, William C., Ossining, NY, UNITED STATES
US 2003092632 A1 20030515
APPLICATION: US 2002-86814 A1 20020228 (10)
PRIORITY: US 2001-272203P 20010228 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a compound comprising the structure: θαYDINYYTSβλ wherein each T represents a threonine, each S represents a serine, each Y represents a tyrosine; each D represents an aspartic acid, each I represents an isoleucine; and each N represents an asparagine; wherein α represents from 0 to 9 amino acids, with the proviso that if there are more than 2 amino acids, they are joined by peptide bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the I at position 9 and extending therefrom in the amino terminal direction; wherein β represents from 0 to 14 amino acids, with the proviso that if there are more than 2 amino acids, they are joined by peptide bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the E at position 18 and extending therefrom in the carboxy terminal direction; wherein θ represents an amino group or an acetylated amino group; wherein λ represents a carboxyl group or an amidated carboxyl group; wherein all of α,Y,D,I,N,Y,Y,T,S and β are joined together by peptide bonds; further provided that at least two tyrosines in the compound are sulfated.
CLM What is claimed is:

1. A compound comprising the structure: θαYDINYYTSp.1am bda. wherein each Y represents a tyrosine; each D represents an aspartic acid, each I represents an isoleucine; and each N represents an asparagine; wherein α represents from 0 to 9 amino acids, with the proviso that if there are more than 2 amino acids, they are joined by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the I at position 9 and extending therefrom in the amino terminal direction; wherein β represents from 0 to 14 amino acids, with the proviso that if there are more than 2 amino acids, they are joined by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the E at position 18 and extending therefrom in the carboxy terminal direction; wherein θ represents an amino group or an acetylated amino group; wherein λ represents a carboxyl group or an amidated carboxyl group; wherein all of α,Y,D,I,N,Y,Y,T,S and β are joined together by **peptide** bonds; further provided that at least two tyrosines in the compound are sulfated.

2. The compound of claim 1, wherein β represents less than 17 amino acids.

3. The compound of claim 1, wherein β represents less than 16 amino acids.

4. The compound of claim 1, wherein β represents less than 15 amino acids.

5. The compound of claim 1, wherein β represents less 10 than 14 amino acids.

6. The compound of claim 1, wherein β represents less than 13 amino acids.

7. The compound of claim 1, wherein β represents less than 12 amino acids.

8. The compound of claim 1, wherein β represents less than 11 amino acids.

9. The compound of claim 1, wherein β represents less than 10 amino acids.

10. The compound of claim 1, wherein β represents less than 9 amino acids.

11. The compound of claim 1, wherein β represents less than 8 amino acids.

12. The compound of claim 1, wherein β represents less than 7 amino acids.

13. The compound of claim 1, wherein β represents less than 6 amino acids.

14. The compound of claim 1, wherein β represents less than 5 amino acids.

15. The compound of claim 1, wherein β represents less than 4 amino acids.

16. The compound of claim 1, wherein β represents less than 3 amino acids.

17. The compound of claim 1, wherein β represents less than 2 amino acids.

18. The compound of claim 1, wherein β represents less than 1 amino acid.

19. The compound of claim 1, wherein α represents less than 9 amino acids.

20. The compound of claim 1, wherein α represents less than 8 amino acids.

21. The compound of claim 1, wherein α represents less than 7 amino acids.

22. The compound of claim 1, wherein α represents less than 6 amino acids.

23. The compound of claim 1, wherein α represents less than 5 amino acids.

24. The compound of claim 1, wherein α represents less than 4 amino acids.

25. The compound of claim 1, wherein α represents less than 3 amino acids.

26. The compound of claim 1, wherein α represents less than 2 amino acids.

27. The compound of claim 1, wherein α represents less than 1 amino acid.

28. A composition comprising the compound of claim 1 and a detectable marker attached thereto.

29. The composition of claim 28, wherein the detectable marker is biotin.

30. The composition of claim 28, wherein the detectable marker is attached at the C-terminus of the compound.

31. A composition which comprises a carrier and an amount of the compound of claim 1 effective to inhibit binding of HIV-1 to a **CCR5** receptor on the surface of a CD4+ cell.

32. A method of inhibiting human immunodeficiency virus infection of a CD4+ cell which also carries a **CCR5** receptor on its surface which comprises contacting the CD4+ cell with an amount of the compound of claim 1 effective to inhibit binding of human immunodeficiency virus to the **CCR5** receptor so as to thereby inhibit human immunodeficiency virus infection of the CD4+ cell.

33. The method of claim 32, wherein the CD4+ cell is present in a subject and the contacting is effected by administering the compound to the subject.

34. A method of preventing CD4+ cells of a subject from becoming infected with human immunodeficiency virus which comprises administering to the subject an amount of the compound of claim 1 effective to inhibit binding of human immunodeficiency virus to **CCR5** receptors on the surface of the CD4+ cells so as to thereby prevent the subject's CD4+ cells from becoming infected with human immunodeficiency virus.

35. A method of treating a subject whose CD4+ cells are infected with human immunodeficiency virus which comprises administering to the subject an amount of the compound of claim 1 effective to inhibit binding of human immunodeficiency virus to **CCR5** receptors on the surface of the subject's CD4+ cells so as to thereby treat the subject.

36. The method of any one of claims 33-35, wherein the compound is administered by aerosol, intravenous, oral or topical route.

37. The method of claim 33 or 35, wherein the subject is infected with HIV-1 prior to administering the compound to the subject.

38. The method of claim 33 or 34, wherein the subject is not infected with HIV-1 prior to administering the compound to the subject.

39. The method of claim 38, wherein the subject is not infected with, but has been exposed to, human immunodeficiency virus.

40. The method of any one of claims 33-35, wherein the effective amount of the compound comprises from about 1.0 ng/kg to about 100 mg/kg body weight of the subject.

41. The method of claim 40, wherein the effective amount of the compound comprises from about 100 ng/kg to about 50 mg/kg body weight of the subject.

42. The method of claim 41, wherein the effective amount of the compound comprises from about 1 μg/kg to about 10 mg/kg body weight of the subject.

43. The method of claim 42, wherein the effective amount of the compound comprises from about 100 μg/kg to about 1 mg/kg body weight of the subject.

44. The method of any one of claims 33-35, wherein the subject is a human being.

45. A method of identifying an agent which inhibits binding of a **CCR5** ligand to a **CCR5** receptor which comprises: (a) immobilizing the compound of claim 1 on a solid support; (b) contacting the immobilized compound from step (a) with sufficient detectable **CCR5** ligand to saturate all binding sites for the **CCR5** ligand on the immobilized compound under conditions permitting binding of the **CCR5** ligand to the immobilized compound so as to form a complex; (c) removing any unbound **CCR5** ligand; (d) contacting the complex from step (b) with the agent; and (e) detecting whether any **CCR5** ligand is displaced from the complex, wherein displacement of detectable **CCR5** ligand from the complex indicates that the agent binds to the compound so as to thereby identify the agent as one which inhibits binding of the **CCR5** ligand to the **CCR5** receptor.

46. A method of identifying an agent which inhibits binding of a **CCR5** ligand to a **CCR5** receptor which comprises: (a) contacting the compound of claim 1 with sufficient detectable **CCR5** ligand to saturate all binding sites for the **CCR5** ligand on the compound under conditions permitting binding of the **CCR5** ligand to the compound so as to form a complex; (b) removing any unbound **CCR5** ligand; (c) measuring the amount of **CCR5** ligand which is bound to the compound in the complex; (d) contacting the complex from step (a) with the agent so as to displace **CCR5** ligand from the complex; (e) measuring the amount of **CCR5** ligand which is bound to the compound in the presence of the agent; and (f) comparing the amount of **CCR5** ligand bound to the compound in step (e) with the amount measured in step (c), wherein a reduced amount measured in step (e) indicates that the agent binds to the compound so as to thereby identify the agent as one which inhibits binding of the **CCR5** ligand to the **CCR5** receptor.

47. A method of identifying an agent which inhibits binding of a **CCR5** ligand to a **CCR5** receptor which comprises: (a) immobilizing the compound of claim 1 on on a solid support; (b) contacting the immobilized compound from step (a) with the agent and detectable **CCR5** ligand under conditions permitting binding of the **CCR5** ligand to the immobilized compound so as to form a complex; (c) removing any unbound **CCR5** ligand; (d) measuring the amount of detectable **CCR5** ligand which is bound to the immobilized compound in the complex; (e) measuring the amount of detectable **CCR5** ligand which binds to the immobilized compound in the absence of the agent; (f) comparing the amount of **CCR5** ligand which is bound to the immobilized compound in step (e) with the amount measured in step (d), wherein a reduced amount measured in step (d) indicates that the agent binds to the compound or **CCR5** ligand so as to thereby identify the agent as one which inhibits binding of the **CCR5** ligand to the **CCR5** receptor.

48. The method of claim 47, wherein the amount of the detectable ligand in step (a) and step (e) is sufficient to saturate all binding sites for the **CCR5** ligand on the compound.

49. A method of identifying an agent which inhibits binding of a **CCR5** ligand to a **CCR5** receptor which comprises: (a) contacting the compound of claim 1 with the agent and detectable **CCR5** ligand under conditions permitting binding of the **CCR5** ligand to the compound so as to form a complex; (b) removing any unbound **CCR5** ligand; (c) measuring the amount of detectable **CCR5** ligand which is bound to the compound in the complex; (d) measuring the amount of detectable **CCR5** ligand which binds to the compound in the absence of the agent; (e) comparing the amount of **CCR5** ligand which is bound to the compound in step (c) with the amount measured in step (d), wherein a reduced amount measured in step (c) indicates that the agent binds to the compound or **CCR5** ligand so as to thereby identify the agent as one which inhibits binding of the **CCR5** ligand to the **CCR5** receptor.

50. The method of claim 49, wherein the amount of the detectable ligand in step (a) and step (d) is sufficient to saturate all binding sites for the **CCR5** ligand on the compound.

51. The method of any one of claims 45-50, wherein the detectable **CCR5** ligand is labeled with a detectable marker.

52. A method of identifying an agent which inhibits binding of a **CCR5** ligand to a **CCR5** receptor which comprises: a) immobilizing the compound of claim 1 on a solid support; b) contacting the immobilized compound from step a) with the agent dissolved or suspended in a known vehicle and measuring the binding signal generated by such contact; c) contacting the immobilized compound from step a) with the known vehicle in the absence of the compound and measuring the binding signal generated by such contact; d) comparing the binding signal measured in step b) with the binding signal measured in step c), wherein an increased amount measured in step b) indicates that the agent binds to the compound so as to thereby identify the agent as one which binds to the **CCR5** receptor.

53. The method of claim 52, wherein the solid support is a surface plasmon resonance sensor chip.

54. The method of claim 52 or 53, wherein the binding signal is measured by surface plasmon resonance.

55. A method of obtaining a composition which comprises: (a) identifying a compound which inhibits binding of a **CCR5** ligand to a **CCR5** receptor according to the method of any one of claims 45-50 and 52; and (b) admixing the compound so identified or a homolog or derivative thereof with a carrier.

56. The method of any one of claims 45-50 and 52, wherein the **CCR5** ligand is a complex comprising an HIV-1 envelope glycoprotein and a CD4-based protein.

57. The method of claim 56, wherein the HIV-1 envelope glycoprotein is gp120, gp140 or gp160.

58. The method of claim 56, wherein the CD4-based protein is soluble CD4 or CD4-IgG2.

59. The method of any one of claims 45-50 and 52, wherein the **CCR5** ligand is a chemokine.

60. The method of claim 59, wherein the chemokine is RANTES, MIP-1α or MIP-1β.

61. The method of any one of claims 45-50 and 52, wherein the **CCR5** ligand is an antibody.

62. The method of claim 61, wherein the antibody is selected from the group consisting of PA8 (ATCC Accession No. HB-12605), PA10 (ATCC Accession No.12607), PA11 (ATCC Accession No. HB-12608), PA12 (ATCC Accession No. HB-12609).

63. The method of claim 45 or 47, wherein the solid support is a microtiter plate well, a bead or surface plasmon resonance sensor chip.

64. A compound having the structure: Δ-$(\alpha YDINYYTS\beta\lambda)_{\pi}$ wherein each T represents a threonine, each S represents a serine, each Y represents a tyrosine; each D represents an aspartic acid, each I represents an isoleucine; and each N represents an asparagine; wherein α represents from 0 to 9 amino acids, with the proviso that if there are more than 2 amino acids, they are joined together by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the I at position 9 and extending therefrom in the amino terminal direction; wherein β represents from 0 to 14 amino acids, with the proviso that if there are more than 2 amino acids, they are joined together by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the E at position 18 and extending therefrom in the carboxy terminal direction; wherein λ represents a carboxyl group or an amidated carboxyl group; wherein all of α,Y,D,I,N,Y,Y,T,S and β are joined together by **peptide** bonds, further provided that at least two tyrosines in the compound are sulfated, wherein π is an integer from 1 to 8, Δ is a polymer, and the solid line represents up to 8 linkers which attach the structure in parentheses to Δ.

65. A compound having the structure: (θαYDINYYTSβ) π-Δ wherein each T represents a threonine, each S represents a serine, each Y represents a tyrosine; each D represents an aspartic acid, each I represents an isoleucine; and each N represents an asparagine; wherein α represents from 0 to 9 amino acids, with the proviso that if there are more than 2 amino acids, they are joined together by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the I at position 9 and extending therefrom in the amino terminal direction; wherein β represents from 0 to 14 amino acids, with the proviso that if there are more than 2 amino acids, they are joined together by **peptide** bonds in consecutive order and have a sequence identical to the sequence set forth in SEQ ID NO: 1 beginning with the E at position 18 and extending therefrom in the carboxy terminal direction; wherein θ represents an amino group or an acetylated amino group; wherein

all of α,Y,D,L,N,Y,Y,T,S and p are joined together by **peptide** bonds, further provided that at least two tyrosines in the compound are sulfated, wherein π is an integer from 1 to 8, Δ is a polymer, and the solid line represents up to 8 linkers which attach the structure in parentheses to Δ.

66. The compound of claim 64 or 65, wherein the polymer is selected from the group consisting of a linear lysine polymer, a branched lysine polymer, a linear arginine polymer, a branched arginine polymer, polyethylene glycol, a linear acetylated lysine polymer, a branched acetylated lysine polymer, a linear chloroacetylated lysine polymer and a branched chloroacetylated lysine polymer.

L10 ANSWER 47 OF 60 USPATFULL on STN
2002:198280 Compositions and methods for inhibition of HIV-1 infection.
Olson, William C., Ossining, NY, UNITED STATES
Maddon, Paul J., Scarsdale, NY, UNITED STATES
US 2002106374 A1 20020808
APPLICATION: US 2001-912824 A1 20010725 (9)
PRIORITY: US 2001-266738P 20010206 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a composition which comprises an admixture of three compounds, wherein: (a) one compound is an antibody which binds to a **CCR5** receptor; (b) one compound retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell; and (c) one compound retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate; wherein the relative mass ratio of any two of the compounds in the admixture ranges from about 100:1 to about 1:100, the composition being effective to inhibit HIV-1 infection of the CD4+ cell. This invention also provides a method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with an amount of the composition of the subject invention effective to inhibit HIV-1 infection of the CD4+ cell so as to thereby inhibit HIV-1 infection of the CD4+ cell.

CLM What is claimed is:

1. A composition which comprises an admixture of two compounds, wherein: (a) one compound is an antibody or portion thereof which binds to a **CCR5** receptor; and (b) one compound retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate; wherein the relative mass ratio of the compounds in the admixture ranges from about 100:1 to about 1:100, the composition being effective to inhibit HIV-1 infection of the CD4+ cell.

2. A composition which comprises an admixture of three compounds, wherein: (a) one compound is an antibody or portion thereof which binds to a **CCR5** receptor; (b) one compound retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell; and (c) one compound retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate; wherein the relative mass ratio of any two of the compounds in the admixture ranges from about 100:1 to about 1:100, the composition being effective to inhibit HIV-1 infection of the CD4+ cell.

3. The composition of claim 2, wherein the compound which retards attachment of HIV-1 to the CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell is a CD4-based protein.

4. The composition of claim 3, wherein the CD4-based protein is a CD4-immunoglobulin fusion protein.

5. The composition of claim 4, wherein the CD4-immunoglobulin fusion protein is CD4-IgG2, wherein the CD4-IgG2 comprises two heavy chains and two lights chains, wherein the heavy chains are encoded by an expression vector designated CD4-IgG2HC-pRcCMV (ATCC Accession No. 75193) and the light chains are encoded by an expression vector designated CD4-kLC-pRcCMV (ATCC Accession No. 75194).

6. The composition of claim 2, wherein the compound which retards attachment of HIV-1 to the CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell is a protein, the amino acid sequence of which comprises that of a protein found in HIV-1 as an envelope glycoprotein.

7. The composition of claim 6, wherein the protein binds to an epitope of CD4 on the surface of the CD4+ cell.

8. The composition of claim 7, wherein the envelope glycoprotein is selected from the group consisting of gp120, gp160, and gp140.

9. The composition of claim 2, wherein the compound which retards the attachment of HIV-1 to the CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell is an antibody or portion of an antibody.

10. The composition of claim 9, wherein the antibody is a monoclonal antibody.

11. The composition of claim 10, wherein the monoclonal antibody is a human, humanized or chimeric antibody.

12. The composition of claim 9, wherein the portion of the antibody is a Fab fragment of the antibody.

13. The composition of claim 9, wherein the portion of the antibody comprises the variable domain of the antibody.

14. The composition of claim 9, wherein the portion of the antibody comprises a CDR portion of the antibody.

15. The composition of claim 10, wherein the monoclonal antibody is an IgG, IgM, IgD, IgA, or IgE monoclonal antibody.

16. The composition of claim 10, wherein the monoclonal antibody binds to an HIV-1 envelope glycoprotein.

17. The composition of claim 16, wherein the HIV-1 envelope glycoprotein is selected from the group consisting of gp120 and gp160.

18. The composition of claim 16, wherein HIV-1 envelope glycoprotein is gp120 and the monoclonal antibody which binds to gp120 is IgG1b12 or F105.

19. The composition of claim 9, wherein the antibody binds to an epitope of CD4 on the surface of the CD4+ cell.

20. The composition of claim 2, wherein the compound which retards attachment of HIV-1 to the CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell is a **peptide**.

21. The composition of claim 2, wherein the compound which retards attachment of HIV-1 to the CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell is a nonpeptidyl agent.

22. The composition of claim 1 or 2, wherein the compound which retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate is an antibody.

23. The composition of claim 22, wherein the antibody is a monoclonal antibody.

24. The composition of claim 1 or 2, wherein the compound which retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate is a **peptide**.

25. The composition of claim 1 or 2, wherein the compound which retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate is a fusion protein which comprises a **peptide** selected from the group consisting of T-20 (SEQ ID NO: 1), DP107 (SEQ ID NO: 2), N34 (SEQ ID NO: 3), C28 (SEQ ID NO: 4), N34(L6)C28 (SEQ ID NO: 5), and T-1249 (SEQ ID NO:6).

26. The composition of claim 24, wherein the **peptide** is selected from the group consisting of T-20 (SEQ ID NO: 1), DP107 (SEQ ID NO: 2), N34 (SEQ ID NO: 3), C28 (SEQ ID NO: 4), N34(L6)C28 (SEQ ID NO: 5), and T-1249 (SEQ ID NO:6).

27. The composition of claim 24, wherein the **peptide** is T-20 (SEQ ID NO: 1).

28. The composition of claim 1 or 2, wherein the compound which retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate is a non-peptidyl agent.

29. The composition of claim 1 or 2, wherein the antibody which binds to a **CCR5** receptor is selected from the group consisting of PA8 (ATCC Accession No. HB-12605), PA10 (ATCC Accession No.12607), PA11 (ATCC Accession No. HB-12608), PA12 (ATCC Accession No. HB-12609), and PA14 (ATCC Accession No. HB-12610).

30. The composition of claim 1 or 2, wherein the antibody is PA14 (ATCC Accession No. HB-12610).

31. The composition of claim 29, wherein the antibody is a monoclonal antibody.

32. The composition of claim 29, wherein the monoclonal antibody is a human, humanized or chimeric antibody.

33. The composition of claim 1 or 2, wherein the portion of the antibody is a Fab fragment of the antibody.

34. The composition of claim 1 or 2, wherein the portion of the antibody comprises the variable domain of the antibody.

35. The composition of claim 1 or 2, wherein the portion of the antibody comprises a CDR portion of the antibody.

36. The composition of claim 31, wherein the monoclonal antibody is an IgG, IgM, IgD, IgA, or IgE monoclonal antibody.

37. The composition of claim 1 or 2, wherein the relative mass ratio of each such compound in the admixture ranges from about 25:1 to about 1:1.

38. The composition of claim 37, wherein the mass ratio is about 25:1

39. The composition of claim 37, wherein the mass ratio is about 5:1.

40. The composition of claim 37, wherein the mass ratio is about 1:1.

41. The composition of claim 1 or 2, wherein the composition is admixed with a carrier.

42. The composition of claim 41, wherein the carrier is an aerosol, intravenous, oral or topical carrier.

43. A method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with an amount of the composition of claim 1 or 2 effective to inhibit HIV-1 infection of the CD4+ cell so as to thereby inhibit HIV-1 infection of the CD4+ cell.

44. The method of claim 43, wherein the CD4+ cell is present in a subject and the contacting is effected by administering the composition to the subject.

45. The method of claim 43, wherein the effective amount of the composition comprises from about 0.000001 mg/kg body weight to about 100 mg/kg body weight of the subject.

46. A method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with (1) an amount of an antibody which binds to a **CCR5** receptor and (2) an amount of a compound which retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate, so as to thereby inhibit HIV-1 infection of the CD4+ cell.

47. A method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with (1) an amount of an antibody which binds to a **CCR5** receptor, (2) an amount of a compound which retards attachment of HIV-1 to the CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell effective to inhibit HIV-1 infection of the CD4+ cell, and (3) an amount of a compound which retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate, so as to thereby inhibit HIV-1 infection of the CD4+ cell.

48. The method of claim 46 or 47, wherein the CD4+ cell is present in a subject and the contacting is effected by administering the compounds to the subject.

49. The method of claim 48, wherein the compounds are administered to the subject simultaneously.

50. The method of claim 48, wherein the compounds are administered to the subject at different times.

51. The method of claim 48, wherein the compounds are administered to the subject by different routes of administration.

=> d his

(FILE 'HOME' ENTERED AT 13:55:02 ON 04 MAR 2004)

FILE 'USPATFULL' ENTERED AT 13:56:10 ON 04 MAR 2004
E SAXINGER CARL/IN
L1 6 S E3 OR E4

FILE 'WPIDS' ENTERED AT 13:57:03 ON 04 MAR 2004

```
                E SAXINGER C/IN
L2              8 S E3 OR E4

     FILE 'MEDLINE' ENTERED AT 13:58:11 ON 04 MAR 2004
                E SAXINGER C/AU
L3             71 S E3 OR E4
L4              0 S L3 AND (CCR5 OR CHEMOKINE RECEPTOR?)
L5             28 S L3 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L6              2 S L5 AND (GP120 OR GP160)

     FILE 'USPATFULL' ENTERED AT 13:59:56 ON 04 MAR 2004
L7           1938 S (CCR5 OR CHEMOKINE RECEPTOR?)
L8           1044 S L7 AND CCR5
L9            163 S L8 AND CCR5/CLM
L10            60 S L9 AND (POLYPEPTIDE?/CLM OR PEPTIDE?/CLM)

=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      43.92      61.89

FILE 'MEDLINE' ENTERED AT 14:04:43 ON 04 MAR 2004

 FILE LAST UPDATED: 3 MAR 2004 (20040303/UP).  FILE COVERS 1953 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s (CCR5 or chemokine receptor?)
           2576 CCR5
           9338 CHEMOKINE
         634468 RECEPTOR?
           3695 CHEMOKINE RECEPTOR?
                  (CHEMOKINE(W)RECEPTOR?)
L11        4916 (CCR5 OR CHEMOKINE RECEPTOR?)

=> s l11 and CCR5
           2576 CCR5
L12        2576 L11 AND CCR5

=> s l12 and (polypeptide? or peptide? or epitope?)
          83239 POLYPEPTIDE?
         347525 PEPTIDE?
          75761 EPITOPE?
L13         354 L12 AND (POLYPEPTIDE? OR PEPTIDE? OR EPITOPE?)

=> s l13 and (HIV or human immunodeficiency virus)
         134297 HIV
        8426654 HUMAN
         112025 IMMUNODEFICIENCY
         369167 VIRUS
          42252 HUMAN IMMUNODEFICIENCY VIRUS
                  (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L14         305 L13 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l14 and (gp120 or gp160 or env?)
           5760 GP120
           1415 GP160
```

```
          346052 ENV?
L15         221 L14 AND (GP120 OR GP160 OR ENV?)

=> s l15 and (inhibit? or antiviral? or antiretrovir?)
       1085924 INHIBIT?
         38766 ANTIVIRAL?
         11583 ANTIRETROVIR?
L16        104 L15 AND (INHIBIT? OR ANTIVIRAL? OR ANTIRETROVIR?)

=> d l16,ti,1-104

L16  ANSWER 1 OF 104      MEDLINE on STN
TI   Specific inhibition of HIV-1 coreceptor activity by synthetic
     peptides corresponding to the predicted extracellular loops of CCR5.

L16  ANSWER 2 OF 104      MEDLINE on STN
TI   Role of the ectodomain of the gp41 transmembrane envelope protein of
     human immunodeficiency virus type 1 in late steps of the membrane
     fusion process.

L16  ANSWER 3 OF 104      MEDLINE on STN
TI   Intrapatient alterations in the human immunodeficiency virus type 1
     gp120 V1V2 and V3 regions differentially modulate coreceptor usage,
     virus inhibition by CC/CXC chemokines, soluble CD4, and the b12 and 2G12
     monoclonal antibodies.

L16  ANSWER 4 OF 104      MEDLINE on STN
TI   Improved breadth and potency of an HIV-1-neutralizing human single-chain
     antibody by random mutagenesis and sequential antigen panning.

L16  ANSWER 5 OF 104      MEDLINE on STN
TI   Neutralization of infectivity of diverse R5 clinical isolates of human
     immunodeficiency virus type 1 by gp120-binding 2'F-RNA aptamers.

L16  ANSWER 6 OF 104      MEDLINE on STN
TI   Genetic and functional analysis of full-length human immunodeficiency
     virus type 1 env genes derived from brain and blood of patients with
     AIDS.

L16  ANSWER 7 OF 104      MEDLINE on STN
TI   The theta-defensin, retrocyclin, inhibits HIV-1 entry.

L16  ANSWER 8 OF 104      MEDLINE on STN
TI   Purified complexes of HIV-1 envelope glycoproteins with CD4 and
     CCR5(CXCR4): production, characterization and immunogenicity.

L16  ANSWER 9 OF 104      MEDLINE on STN
TI   Access of antibody molecules to the conserved coreceptor binding site on
     glycoprotein gp120 is sterically restricted on primary human
     immunodeficiency virus type 1.

L16  ANSWER 10 OF 104     MEDLINE on STN
TI   Inhibitors of the entry of HIV into host cells.

L16  ANSWER 11 OF 104     MEDLINE on STN
TI   CCR5 N-terminus peptides enhance X4 HIV-1 infection by CXCR4
     up-regulation.

L16  ANSWER 12 OF 104     MEDLINE on STN
TI   Tyrosine sulfation of human antibodies contributes to recognition of the
     CCR5 binding region of HIV-1 gp120.

L16  ANSWER 13 OF 104     MEDLINE on STN
TI   The HIV Env-mediated fusion reaction.

L16  ANSWER 14 OF 104     MEDLINE on STN
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TI High frequency of syncytium inducing and CXCR4 tropic viruses among **human immunodeficiency virus** type 1 subtype C-infected patients receiving **antiretroviral** treatment.

L16 ANSWER 15 OF 104 MEDLINE on STN
TI Discordant outcomes following failure of **antiretroviral** therapy are associated with substantial differences in **human immunodeficiency virus**-specific cellular immunity.

L16 ANSWER 16 OF 104 MEDLINE on STN
TI Analysis of the mechanism by which the small-molecule **CCR5** antagonists SCH-351125 and SCH-350581 **inhibit human immunodeficiency virus** type 1 entry.

L16 ANSWER 17 OF 104 MEDLINE on STN
TI Entry **inhibitors** SCH-C, RANTES, and T-20 block **HIV** type 1 replication in multiple cell types.

L16 ANSWER 18 OF 104 MEDLINE on STN
TI The **CCR5** and CXCR4 coreceptors are both used by **human immunodeficiency virus** type 1 primary isolates from subtype C.

L16 ANSWER 19 OF 104 MEDLINE on STN
TI **Human immunodeficiency virus** type 1 attachment, coreceptor, and fusion **inhibitors** are active against both direct and trans infection of primary cells.

L16 ANSWER 20 OF 104 MEDLINE on STN
TI CD4 binding site antibodies **inhibit human immunodeficiency virus gp120 envelope** glycoprotein interaction with **CCR5**.

L16 ANSWER 21 OF 104 MEDLINE on STN
TI Sensitivity of **HIV**-1 to entry **inhibitors** correlates with **envelope**/coreceptor affinity, receptor density, and fusion kinetics.

L16 ANSWER 22 OF 104 MEDLINE on STN
TI Characterization of CD4-induced **epitopes** on the **HIV** type 1 **gp120 envelope** glycoprotein recognized by neutralizing human monoclonal antibodies.

L16 ANSWER 23 OF 104 MEDLINE on STN
TI Evaluation of current approaches to **inhibit HIV** entry.

L16 ANSWER 24 OF 104 MEDLINE on STN
TI Ionic interaction of the **HIV**-1 V3 domain with **CCR5** and deregulation of T lymphocyte function.

L16 ANSWER 25 OF 104 MEDLINE on STN
TI A post-CD4-binding step involving interaction of the V3 region of viral **gp120** with host cell surface glycosphingolipids is common to entry and infection by diverse **HIV**-1 strains.

L16 ANSWER 26 OF 104 MEDLINE on STN
TI Synthetic **peptides** for study of **human immunodeficiency virus** infection.

L16 ANSWER 27 OF 104 MEDLINE on STN
TI Engineered CD4- and CXCR4-using simian immunodeficiency virus from African green monkeys is neutralization sensitive and replicates in nonstimulated lymphocytes.

L16 ANSWER 28 OF 104 MEDLINE on STN
TI Evolution of the gp41 **env** region in **HIV**-infected patients receiving T-20, a fusion **inhibitor**.

L16 ANSWER 29 OF 104 MEDLINE on STN
TI Characterization of the anti-**HIV** effects of native lactoferrin and other

milk proteins and protein derived **peptides**.

L16 ANSWER 30 OF 104 MEDLINE on STN
TI Human alpha-fetoprotein binds to primary macrophages.

L16 ANSWER 31 OF 104 MEDLINE on STN
TI **HIV** receptors and cellular tropism.

L16 ANSWER 32 OF 104 MEDLINE on STN
TI Coreceptor phenotype of natural **human immunodeficiency virus** with nef deleted evolves in vivo, leading to increased virulence.

L16 ANSWER 33 OF 104 MEDLINE on STN
TI Broadly cross-reactive **HIV**-1-neutralizing human monoclonal Fab selected for binding to **gp120**-CD4-**CCR5** complexes.

L16 ANSWER 34 OF 104 MEDLINE on STN
TI Inter-retroviral fusion mediated by **human immunodeficiency virus** or murine leukemia virus glycoproteins: independence of cellular membranes and membrane vesicles.

L16 ANSWER 35 OF 104 MEDLINE on STN
TI Virologic risk factors for vertical transmission of **HIV** type 1 in Puerto Rico.

L16 ANSWER 36 OF 104 MEDLINE on STN
TI Characterization of **HIV** isolates from Puerto Rican maternal-infant pairs reveal predominance of non-syncytium inducing (NSI) variants with **CCR5** genotype.

L16 ANSWER 37 OF 104 MEDLINE on STN
TI Researchers explore new anti-**HIV** agents.

L16 ANSWER 38 OF 104 MEDLINE on STN
TI Multiple active states and oligomerization of **CCR5** revealed by functional properties of monoclonal antibodies.

L16 ANSWER 39 OF 104 MEDLINE on STN
TI Primary intestinal epithelial cells selectively transfer R5 **HIV**-1 to **CCR5**+ cells.

L16 ANSWER 40 OF 104 MEDLINE on STN
TI Receptors for chemotactic formyl **peptides** as pharmacological targets.

L16 ANSWER 41 OF 104 MEDLINE on STN
TI A variable region 3 (V3) mutation determines a global neutralization phenotype and CD4-independent infectivity of a **human immunodeficiency virus** type 1 **envelope** associated with a broadly cross-reactive, primary virus-neutralizing antibody response.

L16 ANSWER 42 OF 104 MEDLINE on STN
TI New developments in anti-**HIV** chemotherapy.

L16 ANSWER 43 OF 104 MEDLINE on STN
TI Katy, bar the door! **HIV** entry **inhibitors**.

L16 ANSWER 44 OF 104 MEDLINE on STN
TI **Gp120**-induced Bob/GPR15 activation: a possible cause of **human immunodeficiency virus** enteropathy.

L16 ANSWER 45 OF 104 MEDLINE on STN
TI Molecular anatomy of **CCR5** engagement by physiologic and viral chemokines and **HIV**-1 **envelope** glycoproteins: differences in primary structural requirements for RANTES, MIP-1 alpha, and vMIP-II Binding.

L16 ANSWER 46 OF 104 MEDLINE on STN

TI Antigenically distinct conformations of CXCR4.

L16 ANSWER 47 OF 104 MEDLINE on STN
TI **Peptide** T **inhibits HIV**-1 infection mediated by the **chemokine receptor**-5 (**CCR5**).

L16 ANSWER 48 OF 104 MEDLINE on STN
TI Sensitivity of **human immunodeficiency virus** type 1 to fusion **inhibitors** targeted to the gp41 first heptad repeat involves distinct regions of gp41 and is consistently modulated by **gp120** interactions with the coreceptor.

L16 ANSWER 49 OF 104 MEDLINE on STN
TI **gp120**: Biologic aspects of structural features.

L16 ANSWER 50 OF 104 MEDLINE on STN
TI Human peripheral blood T cells, monocytes, and macrophages secrete macrophage inflammatory proteins 1alpha and 1beta following stimulation with heat-inactivated Brucella abortus.

L16 ANSWER 51 OF 104 MEDLINE on STN
TI Human alpha1-acid glycoprotein binds to **CCR5** expressed on the plasma membrane of human primary macrophages.

L16 ANSWER 52 OF 104 MEDLINE on STN
TI Biological and genetic characterization of a **human immunodeficiency virus** strain resistant to CXCR4 antagonist T134.

L16 ANSWER 53 OF 104 MEDLINE on STN
TI The synthetic **peptide** WKYMVm attenuates the function of the **chemokine receptors CCR5** and CXCR4 through activation of formyl **peptide** receptor-like 1.

L16 ANSWER 54 OF 104 MEDLINE on STN
TI Mapping the determinants of the **CCR5** amino-terminal sulfopeptide interaction with soluble **human immunodeficiency virus** type 1 **gp120**-CD4 complexes.

L16 ANSWER 55 OF 104 MEDLINE on STN
TI Interaction between **HIV** type 1 glycoprotein 120 and CXCR4 coreceptor involves a highly conserved arginine residue in hypervariable region 3.

L16 ANSWER 56 OF 104 MEDLINE on STN
TI V3 induces in human normal cell populations an accelerated macrophage-mediated proliferation--apoptosis phenomenon of effector T cells when they respond to their cognate antigen.

L16 ANSWER 57 OF 104 MEDLINE on STN
TI Ion channel activation by SPC3, a **peptide** derived from the **HIV**-1 **gp120** V3 loop.

L16 ANSWER 58 OF 104 MEDLINE on STN
TI The possible involvement of CXCR4 in the **inhibition** of **HIV**-1 infection mediated by DP178/gp41.

L16 ANSWER 59 OF 104 MEDLINE on STN
TI Potent, broad-spectrum **inhibition** of **human immunodeficiency virus** type 1 by the **CCR5** monoclonal antibody PRO 140.

L16 ANSWER 60 OF 104 MEDLINE on STN
TI **HIV**-1 gp41 and type I interferon: sequence homology and biological as well as clinical implications.

L16 ANSWER 61 OF 104 MEDLINE on STN
TI Interferon gamma and interleukin 6 modulate the susceptibility of macrophages to **human immunodeficiency virus** type 1 infection.

L16 ANSWER 62 OF 104 MEDLINE on STN
TI A tyrosine-sulfated **peptide** based on the N terminus of **CCR5** interacts with a CD4-enhanced **epitope** of the **HIV**-1 **gp120 envelope** glycoprotein and **inhibits HIV**-1 entry.

L16 ANSWER 63 OF 104 MEDLINE on STN
TI Down-regulation of the **chemokine receptor CCR5** by activation of chemotactic formyl **peptide** receptor in human monocytes.

L16 ANSWER 64 OF 104 MEDLINE on STN
TI Sensitivity of **human immunodeficiency virus** type 1 to the fusion **inhibitor** T-20 is modulated by coreceptor specificity defined by the V3 loop of **gp120**.

L16 ANSWER 65 OF 104 MEDLINE on STN
TI The role of gammadelta T cells in generating **antiviral** factors and beta-chemokines in protection against mucosal simian immunodeficiency virus infection.

L16 ANSWER 66 OF 104 MEDLINE on STN
TI Paramagnetic proteoliposomes containing a pure, native, and oriented seven-transmembrane segment protein, **CCR5**.

L16 ANSWER 67 OF 104 MEDLINE on STN
TI Characterization and **epitope** mapping of neutralizing monoclonal antibodies produced by immunization with oligomeric simian immunodeficiency virus **envelope** protein.

L16 ANSWER 68 OF 104 MEDLINE on STN
TI Characterization of anti-**CCR5** ribozyme-transduced CD34+ hematopoietic progenitor cells in vitro and in a SCID-hu mouse model in vivo.

L16 ANSWER 69 OF 104 MEDLINE on STN
TI Coreceptor-dependent **inhibition** of the cell fusion activity of simian immunodeficiency virus **Env** proteins.

L16 ANSWER 70 OF 104 MEDLINE on STN
TI Specific interaction of **CCR5** amino-terminal domain **peptides** containing sulfotyrosines with **HIV**-1 **envelope** glycoprotein **gp120**.

L16 ANSWER 71 OF 104 MEDLINE on STN
TI Variable sensitivity of **CCR5**-tropic **human immunodeficiency virus** type 1 isolates to **inhibition** by RANTES analogs.

L16 ANSWER 72 OF 104 MEDLINE on STN
TI Coreceptor usage and RANTES sensitivity of non-syncytium-inducing **HIV**-1 isolates obtained from patients with AIDS.

L16 ANSWER 73 OF 104 MEDLINE on STN
TI Monoclonal antibody screening of a phage-displayed random **peptide** library reveals mimotopes of **chemokine receptor CCR5**: implications for the tertiary structure of the receptor and for an N-terminal binding site for **HIV**-1 **gp120**.

L16 ANSWER 74 OF 104 MEDLINE on STN
TI The emerging role of fusion **inhibitors** in **HIV** infection.

L16 ANSWER 75 OF 104 MEDLINE on STN
TI Synthesis of **peptides** mimicking **chemokine receptor CCR5** and their **inhibitory** effects against **HIV**-1 infection.

L16 ANSWER 76 OF 104 MEDLINE on STN
TI A new insight into the role of "old" chemotactic **peptide** receptors FPR and FPRL1: down-regulation of **chemokine receptors CCR5** and CXCR4.

L16 ANSWER 77 OF 104 MEDLINE on STN
TI Sequential CD4-coreceptor interactions in **human immunodeficiency virus** type 1 **Env** function: soluble CD4 activates **Env** for coreceptor-dependent fusion and reveals blocking activities of antibodies against cryptic conserved **epitopes** on **gp120**.

L16 ANSWER 78 OF 104 MEDLINE on STN
TI Nonproductive **human immunodeficiency virus** type 1 infection of human fetal astrocytes: independence from CD4 and major **chemokine receptors**.

L16 ANSWER 79 OF 104 MEDLINE on STN
TI **Peptide** T blocks **GP120/CCR5 chemokine receptor**-mediated chemotaxis.

L16 ANSWER 80 OF 104 MEDLINE on STN
TI VIP and D-ala-**peptide** T-amide release chemokines which prevent **HIV**-1 **GP120**-induced neuronal death.

L16 ANSWER 81 OF 104 MEDLINE on STN
TI Analysis of **HIV**-1 in the cervicovaginal secretions and blood of pregnant and nonpregnant women.

L16 ANSWER 82 OF 104 MEDLINE on STN
TI V3 loop-derived **peptide** SPC3 **inhibits** infection of CD4- and galactosylceramide- cells by LAV-2/B.

L16 ANSWER 83 OF 104 MEDLINE on STN
TI Changes in and discrepancies between cell tropisms and coreceptor uses of **human immunodeficiency virus** type 1 induced by single point mutations at the V3 tip of the **env** protein.

L16 ANSWER 84 OF 104 MEDLINE on STN
TI Shift of clinical **human immunodeficiency virus** type 1 isolates from X4 to R5 and prevention of emergence of the syncytium-inducing phenotype by blockade of CXCR4.

L16 ANSWER 85 OF 104 MEDLINE on STN
TI Role of the **HIV** type 1 glycoprotein 120 V3 loop in determining coreceptor usage.

L16 ANSWER 86 OF 104 MEDLINE on STN
TI Stable exposure of the coreceptor-binding site in a CD4-independent **HIV**-1 **envelope** protein.

L16 ANSWER 87 OF 104 MEDLINE on STN
TI Protective role of beta-chemokines associated with **HIV**-specific Th responses against perinatal **HIV** transmission.

L16 ANSWER 88 OF 104 MEDLINE on STN
TI Differential **inhibition** of **human immunodeficiency virus** type 1 fusion, **gp120** binding, and CC-chemokine activity by monoclonal antibodies to **CCR5**.

L16 ANSWER 89 OF 104 MEDLINE on STN
TI Marked increase in anti-**HIV** activity, as well as **inhibitory** activity against **HIV** entry mediated by CXCR4, linked to enhancement of the binding ability of tachyplesin analogs to CXCR4.

L16 ANSWER 90 OF 104 MEDLINE on STN
TI **Epitope** mapping of **CCR5** reveals multiple conformational states and distinct but overlapping structures involved in chemokine and coreceptor function.

L16 ANSWER 91 OF 104 MEDLINE on STN
TI A functional, discontinuous **HIV**-1 **gp120** C3/C4 domain-derived, branched, synthetic **peptide** that binds to CD4 and **inhibits** MIP-1alpha chemokine binding.

L16 ANSWER 92 OF 104 MEDLINE on STN
TI Increased association of glycoprotein 120-CD4 with **HIV** type 1 coreceptors in the presence of complex-enhanced anti-CD4 monoclonal antibodies.

L16 ANSWER 93 OF 104 MEDLINE on STN
TI Comparison of the antibody repertoire generated in healthy volunteers following immunization with a monomeric recombinant **gp120** construct derived from a **CCR5**/CXCR4-using **human immunodeficiency virus** type 1 isolate with sera from naturally infected individuals.

L16 ANSWER 94 OF 104 MEDLINE on STN
TI Interaction of **human immunodeficiency virus** type 1 **envelope** glycoprotein V3 loop with **CCR5** and CD4 at the membrane of human primary macrophages.

L16 ANSWER 95 OF 104 MEDLINE on STN
TI Interactions among **HIV gp120**, CD4, and CXCR4: dependence on CD4 expression level, **gp120** viral origin, conservation of the **gp120** COOH- and NH2-termini and V1/V2 and V3 loops, and sensitivity to neutralizing antibodies.

L16 ANSWER 96 OF 104 MEDLINE on STN
TI **HIV**-1 **envelope** gp41 is a potent **inhibitor** of chemoattractant receptor expression and function in monocytes.

L16 ANSWER 97 OF 104 MEDLINE on STN
TI Determinants of **human immunodeficiency virus** type 1 **envelope** glycoprotein activation by soluble CD4 and monoclonal antibodies.

L16 ANSWER 98 OF 104 MEDLINE on STN
TI The V3 loop of **human immunodeficiency virus** type-1 **envelope** protein is a high-affinity ligand for immunophilins present in human blood.

L16 ANSWER 99 OF 104 MEDLINE on STN
TI Antigen-specific release of beta-chemokines by anti-**HIV**-1 cytotoxic T lymphocytes.

L16 ANSWER 100 OF 104 MEDLINE on STN
TI **Envelope** glycoproteins from **human immunodeficiency virus** types 1 and 2 and simian immunodeficiency virus can use human **CCR5** as a coreceptor for viral entry and make direct CD4-dependent interactions with this **chemokine receptor**.

L16 ANSWER 101 OF 104 MEDLINE on STN
TI Antibodies to several conformation-dependent **epitopes** of **gp120**/gp41 **inhibit** CCR-5-dependent cell-to-cell fusion mediated by the native **envelope** glycoprotein of a primary macrophage-tropic **HIV**-1 isolate.

L16 ANSWER 102 OF 104 MEDLINE on STN
TI CD4-dependent, antibody-sensitive interactions between **HIV**-1 and its co-receptor CCR-5.

L16 ANSWER 103 OF 104 MEDLINE on STN
TI CD4-induced interaction of primary **HIV**-1 **gp120** glycoproteins with the **chemokine receptor** CCR-5.

L16 ANSWER 104 OF 104 MEDLINE on STN
TI The V3 domain of the **HIV**-1 **gp120 envelope** glycoprotein is critical for chemokine-mediated blockade of infection.

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L16 ANSWER 1 OF 104 MEDLINE on STN
2004055820. PubMed ID: 14576050. Specific **inhibition** of **HIV**-1 coreceptor activity by synthetic **peptides** corresponding to the predicted extracellular loops of **CCR5**. Agrawal Lokesh; VanHorn-Ali Zainab; Berger Edward A; Alkhatib Ghalib. (Department of Microbiology and Immunology and the Walther Cancer Institute, Indiana University School of Medicine, Indianapolis, IN 46202, USA.) Blood, (2004 Feb 15) 103 (4) 1211-7. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB We used synthetic **peptides** to the extracellular loops (ECLs) of **CCR5** to examine **inhibitory** effects on **HIV** infection/fusion with primary leukocytes and cells expressing recombinant **CCR5**. We show for the first time that **peptides** derived from the first, second, or third ECL caused dose-dependent **inhibition** of fusion and infection, although with varying potencies and specificities for **envelope** glycoproteins (**Envs**) from different strains. The first and third ECL **peptides inhibited Envs** from the R5 Ba-L strain and the R5X4 89.6 strain, whereas the second ECL **peptide inhibited** Ba-L but not 89.6 **Env**. None of the **peptides** affected fusion mediated by **Env** from the X4 LAV strain. Fusion mediated by **Envs** from several primary **HIV**-1 isolates was also **inhibited** by the **peptides**. These findings suggest that various **HIV**-1 strains use **CCR5** domains in different ways. Experiments involving **peptide** pretreatment and washing, modulation of the expression levels of **Env** and **CCR5**, analysis of **CCR5 peptide** effects against different coreceptors, and **inhibition** of radiolabeled glycoprotein (gp) 120 binding to **CCR5** suggested that the **peptide**-blocking activities reflect their interactions with **gp120**. The **CCR5**-derived ECL **peptides** thus provide a useful approach to analyze structure-function relationships involved in **HIV**-1 **Env**-coreceptor interactions and may have implications for the design of drugs that **inhibit HIV** infection.

L16 ANSWER 2 OF 104 MEDLINE on STN
2003610850. PubMed ID: 14694113. Role of the ectodomain of the gp41 transmembrane **envelope** protein of **human immunodeficiency virus** type 1 in late steps of the membrane fusion process. Bar Severine; Alizon Marc. (Department of Cell Biology, Institut Cochin, INSERM U567, CNRS UMR8104, 75014 Paris, France.) Journal of virology, (2004 Jan) 78 (2) 811-20. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The membrane fusion process mediated by the gp41 transmembrane **envelope** glycoprotein of the **human immunodeficiency virus** type 1 (**HIV**-1) was addressed by a flow cytometry assay detecting exchanges of fluorescent membrane probes (DiI and DiO) between cells expressing the **HIV**-1 **envelope** proteins (**Env**) and target cells. Double-fluorescent cells were detected when target cells expressed the type of **chemokine receptor**, CXCR4 or **CCR5**, matching the type of **gp120** surface **envelope** protein, X4 or R5, respectively. Background levels of double-fluorescent cells were observed when the **gp120**-receptor interaction was blocked by AMD3100, a CXCR4 antagonist. The L568A mutation in the N-terminal heptad repeat (HR1) of gp41 resulted in parallel **inhibition** of the formation of syncytia and double-fluorescent cells, indicating that gp41 had a direct role in the exchange of fluorescent probes. In contrast, three mutations in the loop region of the gp41 ectodomain, located on either side of the Cys-(X)(5)-Cys motif (W596 M and W610A) or at the distal end of HR1 (D589L), had limited or no apparent effect on membrane lipid mixing between **Env**(+) and target cells, while they blocked formation of syncytia and markedly reduced the exchanges of cytoplasmic fluorescent probes. The loop region could therefore have a direct or indirect role in events occurring after the merging of membranes, such as the formation or dilation of fusion pores. Two types of **inhibitors** of **HIV**-1 entry, the gp41-derived **peptide** T20 and the betulinic acid derivative RPR103611, had limited effects on membrane exchanges at concentrations blocking or markedly reducing syncytium formation. This finding confirmed that T20 can **inhibit** the late steps of membrane fusion (post-lipid mixing) and brought forth an indirect argument for the role of the gp41 loop region in these steps, as

mutations conferring resistance to KRH0501IV were mapped in this region (I595S or L602H).

L16 ANSWER 3 OF 104 MEDLINE on STN

2003589653. PubMed ID: 14671134. Intrapatient alterations in the **human immunodeficiency virus** type 1 **gp120** V1V2 and V3 regions differentially modulate coreceptor usage, virus **inhibition** by CC/CXC chemokines, soluble CD4, and the b12 and 2G12 monoclonal antibodies. Nabatov Alexey A; Pollakis Georgios; Linnemann Thomas; Kliphius Aletta; Chalaby Moustapha I M; Paxton William A. (Department of Human Retrovirology, Academic Medical Center, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands.) Journal of virology, (2004 Jan) 78 (1) 524-30. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We studied **human immunodeficiency virus** type 1 (**HIV**-1) chimeric viruses altering in their **gp120** V1V2 and V3 **envelope** regions to better map which genetic alterations are associated with specific virus phenotypes associated with **HIV**-1 disease progression. The V1V2 and V3 regions studied were based on viruses isolated from an individual with progressing **HIV**-1 disease. Higher V3 charges were linked with CXCR4 usage, but only when considered within a specific V1V2 and V3 N-linked glycosylation context. When the virus gained R5X4 dual tropism, irrespective of its V3 charge, it became highly resistant to **inhibition** by RANTES and highly sensitive to **inhibition** by SDF-1alpha. R5 viruses with higher positive V3 charges were more sensitive to **inhibition** by RANTES, while R5X4 dualtropic viruses with higher positive V3 charges were more resistant to **inhibition** by SDF-1alpha. Loss of the V3 N-linked glycosylation event rendered the virus more resistant to **inhibition** by SDF-1alpha. The same alterations in the V1V2 and V3 regions influenced the extent to which the viruses were neutralized with soluble CD4, as well as monoclonal antibodies b12 and 2G12, but not monoclonal antibody 2F5. These results further identify a complex set of alterations within the V1V2 and V3 regions of **HIV**-1 that can be selected in the host via alterations of coreceptor usage, CC/CXC chemokine **inhibition**, CD4 binding, and antibody neutralization.

L16 ANSWER 4 OF 104 MEDLINE on STN

2003580202. PubMed ID: 14659751. Improved breadth and potency of an **HIV**-1-neutralizing human single-chain antibody by random mutagenesis and sequential antigen panning. Zhang Mei Yun; Shu Yuuei; Rudolph Donna; Prabakaran Ponraj; Labrijn Aran F; Zwick Michael B; Lal Renu B; Dimitrov Dimiter S. (Human Immunovirology and Computational Biology Group, LECB, CCR, National Cancer Institute-Frederick, NIH, Frederick, MD 21702, USA.) Journal of molecular biology, (2004 Jan 2) 335 (1) 209-19. Journal code: 2985088R. ISSN: 0022-2836. Pub. country: England: United Kingdom. Language: English.

AB Several human monoclonal antibodies can neutralize a range of **human immunodeficiency virus** type 1 (**HIV**-1) primary isolates but their potency and related ability to suppress generation of **HIV**-1 escape mutants is significantly lower than the activity of **antiretroviral** drugs currently in clinical use. Recently, a human Fab, X5, was identified and found to neutralize primary isolates from different clades. Further improvement of the potency and breadth of **HIV**-1 neutralization by this antibody could be critical for its potential use in the treatment of **HIV**-1-infected patients. However, increasing potency of an antibody by selection from libraries may lead to a decrease in the breadth of neutralization. In an attempt to solve this problem, we subjected a random mutagenesis library of the scFv X5 to sequential rounds of selection on non-homologous **HIV**-1 **envelope** glycoproteins (**Envs**) dubbed sequential antigen panning (SAP). By using SAP, we identified two scFv antibodies, m6 and m9, that were tested with a panel of 33 diverse primary **HIV**-1 infectious isolates in an assay based on a reporter cell-line expressing high levels of CD4, **CCR5** and CXCR4. The IC(50) was less than 50 microg/ml for 21 (m6) and 19 (m9) out of 29 isolates from group M (subtypes A-C, F, G and CRF-01AE) and one isolate from group N; three isolates from group O were not significantly **inhibited** at 50

microg/ml. The average IC(90) values for the two antibodies were significantly ($p<0.001$, $n=29$) lower compared to scFv X5. Their **inhibitory** activity does not appear to be related to the **HIV**-1 subtype, coreceptor usage or the disease stage. m9 **inhibited** infection of peripheral blood mononuclear cells by the primary isolates JRCSF, 89.6 and BR020 with IC(90) of 4, 6 and 25 microg/ml, respectively; for a single-round infection by pseudovirus, the IC(90) for JRSCF, 89.6, YU2 and HXBc2 was 15, 5, 15 and 5 microg/ml, respectively. In these two assays the IC(90) for m9 was, on average, two- to threefold lower than for scFv X5. These results demonstrate that both the potency and the breadth of **HIV**-1 neutralization of one of the few known potent broadly cross-reactive human monoclonal antibodies, scFv X5, could be improved significantly. However, only experiments in animal models and clinical trials in humans will show whether these new scFvs and the approach for their identification have potential in the development of prophylactics and therapeutics for **HIV**-1 infections.

L16 ANSWER 5 OF 104 MEDLINE on STN

2003532451. PubMed ID: 14610191. Neutralization of infectivity of diverse R5 clinical isolates of **human immunodeficiency virus** type 1 by **gp120**-binding 2'F-RNA aptamers. Khati Makobetsa; Schuman Michael; Ibrahim Jamal; Sattentau Quentin; Gordon Siamon; James William. (Sir William Dunn School of Pathology, University of Oxford, Oxford OX1 3RE, United Kingdom.) Journal of virology, (2003 Dec) 77 (23) 12692-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** type 1 (**HIV**-1) has evolved a number of strategies to resist current **antiretroviral** drugs and the selection pressures of humoral and cellular adaptive immunity. For example, R5 strains, which use the **CCR5** coreceptor for entry and are the dominant viral phenotype for **HIV**-1 transmission and AIDS pathogenesis, are relatively resistant to neutralization by antibodies, as are other clinical isolates. In order to overcome these adaptations, we raised nucleic acid aptamers to the SU glycoprotein (**gp120**) of the R5 strain, **HIV**-1(Ba-L). These not only bound **gp120** with high affinity but also neutralized **HIV**-1 infectivity in human peripheral blood mononuclear cells (PBMCs) by more than 1,000-fold. Furthermore, these aptamers were able to neutralize the infectivity of R5 clinical isolates of **HIV**-1 derived from group M (subtypes A, C, D, E, and F) and group O. One aptamer defined a site on **gp120** that overlaps partially with the conserved, **chemokine receptor**-binding, CD4-induced **epitope** recognized by monoclonal antibody 17b. In contrast to the antibody, the site is accessible to aptamer in the absence of CD4 binding. Neutralizing aptamers such as this could be exploited to provide leads in developing alternative, efficacious anti-**HIV**-1 drugs and lead to a deeper understanding of the molecular interactions between the virus and its host cell.

L16 ANSWER 6 OF 104 MEDLINE on STN

2003520646. PubMed ID: 14581570. Genetic and functional analysis of full-length **human immunodeficiency virus** type 1 **env** genes derived from brain and blood of patients with AIDS. Ohagen Asa; Devitt Amy; Kunstman Kevin J; Gorry Paul R; Rose Patrick P; Korber Bette; Taylor Joann; Levy Robert; Murphy Robert L; Wolinsky Steven M; Gabuzda Dana. (Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Boston, Massachusetts, USA.) Journal of virology, (2003 Nov) 77 (22) 12336-45. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The genetic evolution of **human immunodeficiency virus** type 1 (**HIV**-1) in the brain is distinct from that in lymphoid tissues, indicating tissue-specific compartmentalization of the virus. Few primary **HIV**-1 **envelope** glycoproteins (**Envs**) from uncultured brain tissues have been biologically well characterized. In this study, we analyzed 37 full-length **env** genes from uncultured brain biopsy and blood samples from four patients with AIDS. Phylogenetic analysis of intrapatient sequence sets showed distinct clustering of brain relative to blood **env**

sequences. However, no brain specific signature sequence was identified. Furthermore, there was no significant difference in the number or positions of N-linked glycosylation sites between brain and blood **env** sequences. The patterns of coreceptor usage were heterogeneous, with no clear distinction between brain and blood **env** clones. Nine **Envs** used **CCR5** as a coreceptor, one used CXCR4, and two used both **CCR5** and CXCR4 in cell-to-cell fusion assays. Eight **Envs** could also use CCR3, CCR8, GPR15, STRL33, Apj, and/or GPR1, but these coreceptors did not play a major role in virus entry into microglia. Recognition of **epitopes** by the 2F5, T30, AG10H9, F105, 17b, and C11 monoclonal antibodies varied among **env** clones, reflecting genetic and conformational heterogeneity. **Envs** from two patients contained 28 to 32 N-glycosylation sites in **gp120**, compared to around 25 in lab strains and well-characterized primary isolates. These results suggest that **HIV**-1 **Envs** in brain cannot be distinguished from those in blood on the basis of coreceptor usage or the number or positions of N-glycosylation sites, indicating that other properties underlie neurotropism. The study also demonstrates characteristics of primary **HIV**-1 **Envs** from uncultured tissues and implies that **Env** variants that are glycosylated more extensively than lab strains and well-characterized primary isolates should be considered during development of vaccines and neutralizing antibodies.

L16 ANSWER 7 OF 104 MEDLINE on STN

2003508590. PubMed ID: 14585219. The theta-defensin, retrocyclin, **inhibits HIV**-1 entry. Munk Carsten; Wei Ge; Yang Otto O; Waring Alan J; Wang Wei; Hong Teresa; Lehrer Robert I; Landau Nathaniel R; Cole Alexander M. (Infectious Disease Laboratory, Salk Institute for Biological Studies, San Diego, CA 92037, USA.) AIDS research and human retroviruses, (2003 Oct) 19 (10) 875-81. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Retrocyclin is a circular antimicrobial 18-residue **peptide** encoded in the human genome by a theta-defensin pseudogene. In the human genome, the gene for retrocyclin is inactivated by an in-frame stop codon in its signal sequence but its mature coding sequence is intact. The **peptide** corresponding to the processed human retrocyclin, generated by solid phase **peptide** synthesis, **inhibited** replication of R5 and X4 strains of **HIV**-1 in human cells. Luciferase reporter virus and Vpr-BLaM entry assays were used to demonstrate that retrocyclin specifically blocked R5 and X4 **HIV**-1 replication at entry. Surface plasmon resonance demonstrated that retrocyclin bound to soluble CD4 and **gp120**, but **gp120** cell-binding assays revealed that retrocyclin did not fully **inhibit** the binding of soluble CD4 to **gp120**. A fluorescent retrocyclin congener localized in cell-surface patches either alone or colocalized with CD4, CXCR4, and **CCR5**. In the aggregate, these results suggest that retrocyclin blocks an entry step in **HIV**-1 replication. Retrocyclin represents a new class of small molecule **HIV**-1 entry **inhibitors**.

L16 ANSWER 8 OF 104 MEDLINE on STN

2003446252. PubMed ID: 14505910. Purified complexes of **HIV**-1 **envelope** glycoproteins with CD4 and **CCR5**(CXCR4): production, characterization and immunogenicity. Xiao Xiaodong; Phogat Sanjay; Shu Yuuei; Phogat Adhuna; Chow Yen Hung; Wei Olivia L; Goldstein Harris; Broder Christopher C; Dimitrov Dimiter S. (Laboratory of Experimental and Computational Biology, National Cancer Institute-Frederick, NIH, Bldg 469, Rm 246, P.O. Box B, Miller Drive, Frederick, MD 21702-1201, USA.) Vaccine, (2003 Oct 1) 21 (27-30) 4275-84. Journal code: 8406899. ISSN: 0264-410X. Pub. country: Netherlands. Language: English.

AB The ability to readily elicit broadly neutralizing antibodies to **HIV**-1 remains elusive. We and others have hypothesized that interaction of the viral **envelope** glycoprotein (**Env**, **gp120**-gp41) with its receptor molecules could enhance the exposure of conserved **epitopes** that may facilitate the elicitation of broadly neutralizing antibodies. The **Env**-CD4-coreceptor complexes mediate **HIV**-1 entry into cells and serve as a major target for **inhibitors** of this process. To begin to evaluate their potential also as vaccine immunogens we produced relatively large

amounts of complexes of purified recombinant soluble truncated **Env**, gp140(89.6) or **gp120**(89.6), with CD4 and **CCR5** or CXCR4. We found that gp140(**gp120**)-CD4-**CCR5** complexes are stable and immunogenic in mice transgenic for human CD4 and **CCR5**. They elicited anti-**gp120** and anti-gp140 antibodies that **inhibited** an heterologous primary **HIV**-1 isolate (JR-FL) with two- to threefold higher neutralizing activity than those elicited by **gp120** and gp140. The antibodies elicited by the complexes competed better with the antibodies X5 and CG10 but not with b12 for binding to **gp120** and **gp120**-CD4 complexes compared to those elicited with gp140(120) alone. These findings suggest that stable purified **Env**-CD4-**CCR5**(CXCR4) complexes can be produced in relatively large amount sufficient for their further characterization that may help in the development of novel vaccines candidates.

L16 ANSWER 9 OF 104 MEDLINE on STN

2003445221. PubMed ID: 12970440. Access of antibody molecules to the conserved coreceptor binding site on glycoprotein **gp120** is sterically restricted on primary **human immunodeficiency virus** type 1. Labrijn Aran F; Poignard Pascal; Raja Aarti; Zwick Michael B; Delgado Karla; Franti Michael; Binley James; Vivona Veronique; Grundner Christoph; Huang Chih-Chin; Venturi Miro; Petropoulos Christos J; Wrin Terri; Dimitrov Dimiter S; Robinson James; Kwong Peter D; Wyatt Richard T; Sodroski Joseph; Burton Dennis R. (Department of Immunology, The Scripps Research Institute, La Jolla, California 92037, USA.) Journal of virology, (2003 Oct) 77 (19) 10557-65. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Anti-**human immunodeficiency virus** type 1 (**HIV**-1) antibodies whose binding to **gp120** is enhanced by CD4 binding (CD4i antibodies) are generally considered nonneutralizing for primary **HIV**-1 isolates. However, a novel CD4i-specific Fab fragment, X5, has recently been found to neutralize a wide range of primary isolates. To investigate the precise nature of the extraordinary neutralizing ability of Fab X5, we evaluated the abilities of different forms (immunoglobulin G [IgG], Fab, and single-chain Fv) of X5 and other CD4i monoclonal antibodies to neutralize a range of primary **HIV**-1 isolates. Our results show that, for a number of isolates, the size of the neutralizing agent is inversely correlated with its ability to neutralize. Thus, the poor ability of CD4i-specific antibodies to neutralize primary isolates is due, at least in part, to steric factors that limit antibody access to the **gp120** **epitopes**. Studies of temperature-regulated neutralization or fusion-arrested intermediates suggest that the steric effects are important in limiting the binding of IgG to the viral **envelope** glycoproteins after **HIV**-1 has engaged CD4 on the target cell membrane. The results identify hurdles in using CD4i **epitopes** as targets for antibody-mediated neutralization in vaccine design but also indicate that the CD4i regions could be efficiently targeted by small molecule entry **inhibitors**.

L16 ANSWER 10 OF 104 MEDLINE on STN

2003413093. PubMed ID: 12951808. **Inhibitors** of the entry of **HIV** into host cells. Meanwell Nicholas A; Kadow John F. (Bristol-Myers Squibb Pharmaceutical Research Institute, Department of Chemistry, 5 Research Parkway, Wallingford, CT 06492, USA.. Nicholas.Meanwell@bms.com) . Current opinion in drug discovery & development, (2003 Jul) 6 (4) 451-61. Ref: 99. Journal code: 100887519. ISSN: 1367-6733. Pub. country: England: United Kingdom. Language: English.

AB The development of mechanistic insight into the process by which **HIV** enters host cells has revealed a panoply of targets that offer considerable potential as sites for pharmacological intervention. The **gp120**/gp41 protein complex, expressed on the virion surface, mediates **HIV** entry by a process initiated by the engagement of the host cell receptor CD4. Subtle conformational changes triggered by this interaction expose elements of **gp120** to the seven-transmembrane, G protein-coupled **chemokine receptors CCR5** or CXCR4 expressed on host cells, a contact that relieves constraints imposed on gp41 by **gp120**. This leads to a major conformational rearrangement of gp41, which results in the insertion

of the fusion **peptide** into the host cell membrane and the assembly of the amino terminus heptad repeat into a trimeric form that is subsequently recognized by the carboxy terminal heptad repeat. The latter process leads to juxtaposition of the viral and host cell membranes, a prelude to fusion. The most prominent strategies and targets that are actively being exploited as drug discovery opportunities are **inhibition** of the attachment of **HIV** to host cells, blockade of **chemokine receptors** and interference with the function of gp41. **Inhibitors** of each of these steps in the **HIV** entry process with potential clinical relevance are reviewed in the context of their status in the drug development process. The most significant entity to emerge from this area of research to date is enfuvirtide, a 36-amino acid derivative that interferes with the function of gp41. Enfuvirtide is the first **HIV** entry **inhibitor** to be granted a license for marketing (it was approved in the US and Europe in March 2003), and its introduction portends the beginning of what promises to be an exciting new era of **HIV** therapy.

L16 ANSWER 11 OF 104 MEDLINE on STN
2003360075. PubMed ID: 12893271. **CCR5** N-terminus **peptides** enhance X4 **HIV**-1 infection by CXCR4 up-regulation. Dettin M; Zanchetta M; Pasquato A; Borrello M; Piatier-Tonneau D; Di Bello C; De Rossi A. (Department of Chemical Process Engineering, University of Padova, 35131 Padova, Italy.. monica.dettin@unipd.it) . Biochemical and biophysical research communications, (2003 Aug 1) 307 (3) 640-6. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.
AB The **HIV**-1 **envelope** glycoprotein **gp120** interacts consecutively with CD4 and **CCR5** to mediate the entry of R5-**HIV**-1 strains into target cells. The N-terminus of **CCR5**, which contains several sulfated tyrosines, plays a critical role in **gp120**-**CCR5** binding and, consequently, in viral entry. Here, we demonstrate that a tyrosine sulfated **peptide**, reproducing the entire N-terminal extracellular region of **CCR5**, its unsulfated analogue, and a point-mutated **peptide** are unable to **inhibit** R5-**HIV**-1 mediated infection, competing with the entire **CCR5** in the formation of **gp120**-CD4-**CCR5** complex. Surprisingly, these **peptides** show the capability of enhancing **HIV**-1 infection caused by X4 strains through the up-regulation of both CD4 and CXCR4 receptors.

L16 ANSWER 12 OF 104 MEDLINE on STN
2003355282. PubMed ID: 12887918. Tyrosine sulfation of human antibodies contributes to recognition of the **CCR5** binding region of **HIV**-1 **gp120**. Choe Hyeryun; Li Wenhui; Wright Paulette L; Vasilieva Natalya; Venturi Miro; Huang Chih-Chin; Grundner Christoph; Dorfman Tatyana; Zwick Michael B; Wang Liping; Rosenberg Eric S; Kwong Peter D; Burton Dennis R; Robinson James E; Sodroski Joseph G; Farzan Michael. (Children's Hospital, Department of Pediatrics, Harvard Medical School, Boston, MA 02115, USA.) Cell, (2003 Jul 25) 114 (2) 161-70. Journal code: 0413066. ISSN: 0092-8674. Pub. country: United States. Language: English.
AB Sulfated tyrosines at the amino terminus of the principal **HIV**-1 coreceptor **CCR5** play a critical role in its ability to bind the **HIV**-1 **envelope** glycoprotein **gp120** and mediate **HIV**-1 infection. Here, we show that a number of human antibodies directed against **gp120** are tyrosine sulfated at their antigen binding sites. Like that of **CCR5**, antibody association with **gp120** is dependent on sulfate moieties, enhanced by CD4, and **inhibited** by sulfated **CCR5**-derived **peptides**. Most of these antibodies preferentially associate with **gp120** molecules of **CCR5**-utilizing (R5) isolates and neutralize primary R5 isolates more efficiently than laboratory-adapted isolates. These studies identify a distinct subset of CD4-induced **HIV**-1 neutralizing antibodies that closely emulate **CCR5** and demonstrate that tyrosine sulfation can contribute to the potency and diversity of the human humoral response.

L16 ANSWER 13 OF 104 MEDLINE on STN
2003341455. PubMed ID: 12873764. The **HIV Env**-mediated fusion reaction. Gallo Stephen A; Finnegan Catherine M; Viard Mathias; Raviv Yossef; Dimitrov Antony; Rawat Satinder S; Puri Anu; Durell Stewart; Blumenthal

Robert. (Laboratory of Experimental and Computational Biology, Center for Cancer Research, NCI-Frederick, National Institute of Health, Miller Drive, Frederick, MD 21702-1201, USA.) Biochimica et biophysica acta, (2003 Jul 11) 1614 (1) 36-50. Ref: 168. Journal code: 0217513. ISSN: 0006-3002. Pub. country: Netherlands. Language: English.

AB The current general model of **HIV** viral entry involves the binding of the trimeric viral **envelope** glycoprotein **gp120**/gp41 to cell surface receptor CD4 and chemokine co-receptor CXCR4 or **CCR5**, which triggers conformational changes in the **envelope** proteins. **Gp120** then dissociates from gp41, allowing for the fusion **peptide** to be inserted into the target membrane and the pre-hairpin configuration of the ectodomain to form. The C-terminal heptad repeat region and the leucine/isoleucine zipper region then form the thermostable six-helix coiled-coil, which drives the membrane merger and eventual fusion. This model needs updating, as there has been a wealth of data produced in the last few years concerning **HIV** entry, including target cell dependencies, fusion kinetic data, and conformational intermediates. A more complete model must include the involvement of membrane microdomains, actin polymerization, glycosphingolipids, and possibly CD4 and chemokine signaling in entry. In addition, kinetic experiments involving the addition of fusion **inhibitors** have revealed some of the rate-limiting steps in this process, adding a temporal component to the model. A review of these data that may require an updated version of the original model is presented here.

L16 ANSWER 14 OF 104 MEDLINE on STN

2003313338. PubMed ID: 12805470. High frequency of syncytium-inducing and CXCR4-tropic viruses among **human immunodeficiency virus** type 1 subtype C-infected patients receiving **antiretroviral** treatment. Johnston Elizabeth R; Zijenah Lynn S; Mutetwa Solomon; Kantor Rami; Kittinunvorakoon Chonticha; Katzenstein David A. (Division of Infectious Diseases and AIDS Research, Stanford University, Stanford, California 94035, USA.. betsyj@stanford.edu) . Journal of virology, (2003 Jul) 77 (13) 7682-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** type 1 (**HIV**-1) subtype C viruses have been found to almost exclusively use the **chemokine receptor CCR5** as a coreceptor for entry, even in patients with advanced AIDS. We have characterized subtype C virus isolates from 28 patients from Harare, Zimbabwe, 20 of whom were receiving **antiretroviral** treatment. Virus from 10 of the treated patients induced syncytium formation (SI virus) when cultured with MT2 cells. Only non-syncytium-inducing (NSI) virus was cultured from the peripheral blood mononuclear cells of the eight patients who had not received treatment. The majority of these subtype C SI viruses were capable of using both **CCR5** and CXCR4 as coreceptors for viral entry, and the consensus V3 loop sequences from the SI viruses displayed a high net charge compared to those of NSI viruses. While those on treatment had reverse transcriptase (RT) and protease mutations, there was no clear association between RT and protease drug resistance mutations and coreceptor tropism. These results suggest that CXCR4-tropic viruses are present within the quasispecies of patients infected with subtype C virus and that **antiretroviral** treatment may create an **environment** for the emergence of CXCR4 tropism.

L16 ANSWER 15 OF 104 MEDLINE on STN

2003216064. PubMed ID: 12719595. Discordant outcomes following failure of **antiretroviral** therapy are associated with substantial differences in **human immunodeficiency virus**-specific cellular immunity. Price David A; Scullard George; Oxenius Annette; Braganza Ruth; Beddows Simon A; Kazmi Shamim; Clarke John R; Johnson Gabriele E; Weber Jonathan N; Phillips Rodney E. (The Peter Medawar Building for Pathogen Research and the Nuffield Department of Clinical Medicine, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, United Kingdom.) Journal of virology, (2003 May) 77 (10) 6041-9. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Many individuals chronically infected with **human immunodeficiency**

virus type 1 (HIV-1) experience a recrudescence of plasma virus during continuous combination **antiretroviral** therapy (ART) due either to the emergence of drug-resistant viruses or to poor compliance. In most cases, virologic failure on ART is associated with a coincident decline in CD4(+) T lymphocyte levels. However, a proportion of discordant individuals retain a stable or even increasing CD4(+) T lymphocyte count despite virological failure. In order to address the nature of these different outcomes, we evaluated virologic and immunologic variables in a prospective, single-blinded, nonrandomized cohort of 53 subjects with chronic **HIV**-1 infection who had been treated with continuous ART and monitored intensively over a period of 19 months. In all individuals with detectable viremia on ART, multiple drug resistance mutations with similar impacts on viral growth kinetics were detected in the pol gene of circulating plasma virus. Further, C2V3 **env** gene analysis demonstrated sequences indicative of **CCR5** coreceptor usage in the majority of those with detectable plasma viremia. In contrast to this homogeneous virologic pattern, comprehensive screening with a range of antigens derived from **HIV**-1 revealed substantial immunologic differences. Discordant subjects with stable CD4(+) T lymphocyte counts in the presence of recrudescent virus demonstrated potent virus-specific CD4(+) and CD8(+) T lymphocyte responses. In contrast, subjects with virologic failure associated with declining CD4(+) T lymphocyte counts had substantially weaker **HIV**-specific CD4(+) T lymphocyte responses and exhibited a trend towards weaker **HIV**-specific CD8(+) T lymphocyte responses. Importantly the CD4(+) response was sustained over periods as long as 11 months, confirming the stability of the phenomenon. These correlative data lead to the testable hypothesis that the consequences of viral recrudescence during continuous ART are modulated by the **HIV**-specific cellular immune response.

L16 ANSWER 16 OF 104 MEDLINE on STN

2003190958. PubMed ID: 12692222. Analysis of the mechanism by which the small-molecule **CCR5** antagonists SCH-351125 and SCH-350581 **inhibit human immunodeficiency virus** type 1 entry. Tsamis Fotini; Gavrilov Svetlana; Kajumo Francis; Seibert Christoph; Kuhmann Shawn; Ketas Tom; Trkola Alexandra; Palani Anadan; Clader John W; Tagat Jayaram R; McCombie Stuart; Baroudy Bahige; Moore John P; Sakmar Thomas P; Dragic Tatjana. (Microbiology and Immunology Department, Albert Einstein College of Medicine, Bronx, New York 10461, USA.) Journal of virology, (2003 May) 77 (9) 5201-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** type 1 (**HIV**-1) entry is mediated by the consecutive interaction of the **envelope** glycoprotein **gp120** with CD4 and a coreceptor such as **CCR5** or CXCR4. The **CCR5** coreceptor is used by the most commonly transmitted **HIV**-1 strains that often persist throughout the course of infection. Compounds targeting **CCR5**-mediated entry are a novel class of drugs being developed to treat **HIV**-1 infection. In this study, we have identified the mechanism of action of two **inhibitors** of **CCR5** function, SCH-350581 (AD101) and SCH-351125 (SCH-C). AD101 is more potent than SCH-C at **inhibiting HIV**-1 replication in primary lymphocytes, as well as viral entry and **gp120** binding to cell lines. Both molecules also block the binding of several anti-**CCR5** monoclonal antibodies that recognize **epitopes** in the second extracellular loop of **CCR5**. Alanine mutagenesis of the transmembrane domain of **CCR5** suggests that AD101 and SCH-C bind to overlapping but nonidentical sites within a putative ligand-binding cavity formed by transmembrane helices 1, 2, 3, and 7. We propose that the binding of small molecules to the transmembrane domain of **CCR5** may disrupt the conformation of its extracellular domain, thereby **inhibiting** ligand binding to **CCR5**.

L16 ANSWER 17 OF 104 MEDLINE on STN

2003170689. PubMed ID: 12689409. Entry **inhibitors** SCH-C, RANTES, and T-20 block **HIV** type 1 replication in multiple cell types. Ketas Thomas J; Klasse Per Johan; Spenlehauer Catherine; Nesin Mirjana; Frank Ines; Pope Melissa; Strizki Julie M; Reyes Gregory R; Baroudy Bahige M; Moore

John P. (Department of Microbiology and Immunology, Weill Medical College of Cornell University, New York, New York 10021, USA.) AIDS research and human retroviruses, (2003 Mar) 19 (3) 177-86. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB The small-molecule **CCR5** antagonist SCH-C (SCH 351125) was tested for its ability to **inhibit HIV**-1 replication in peripheral blood mononuclear cells (PBMCs), cord blood mononuclear cells, immature dendritic cells (DCs), and macrophages. **Inhibition** of infection of PBMCs by virus associated with mature DC in trans was also studied. For comparison, the **peptide**-based fusion **inhibitor** T-20 and the CC-chemokine RANTES were also evaluated. Although some cell type-dependent differences in potency were observed, each of the three entry **inhibitors** was active against the replication of three different **CCR5**-using primary isolates in each cell type. **CCR5**-dependent **HIV**-1 infectivity, whether DC associated or not, is thus vulnerable to **inhibitors** that block the virus-cell fusion process by different mechanisms. Together, these results suggest that SCH-C and other entry **inhibitors** should be evaluated for their clinical potential as **inhibitors** of **HIV**-1 replication in several settings, including the prevention of maternal-infant transmission and the prevention of sexual transmission by topical application as a microbicide.

L16 ANSWER 18 OF 104 MEDLINE on STN

2003137893. PubMed ID: 12634405. The **CCR5** and CXCR4 coreceptors are both used by **human immunodeficiency virus** type 1 primary isolates from subtype C. Cilliers Tonie; Nhlapo Jabulani; Coetzer Mia; Orlovic Dragana; Ketas Thomas; Olson William C; Moore John P; Trkola Alexandra; Morris Lynn. (AIDS Virus Research Unit, National Institute for Communicable Diseases, Johannesburg, South Africa.) Journal of virology, (2003 Apr) 77 (7) 4449-56. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** type 1 (**HIV**-1) subtype C viruses with different coreceptor usage profiles were isolated from 29 South African patients with advanced AIDS. All 24 R5 isolates were **inhibited** by the **CCR5**-specific agents, PRO 140 and RANTES, while the two X4 viruses and the three R5X4 viruses were sensitive to the CXCR4-specific **inhibitor**, AMD3100. The five X4 or R5X4 viruses were all able to replicate in peripheral blood mononuclear cells that did not express **CCR5**. When tested using coreceptor-transfected cell lines, one R5 virus was also able to use CXCR6, and another R5X4 virus could use CCR3, BOB/GPR15, and CXCR6. The R5X4 and X4 viruses contained more-diverse V3 loop sequences, with a higher overall positive charge, than the R5 viruses. Hence, some **HIV**-1 subtype C viruses are able to use **CCR5**, CXCR4, or both CXCR4 and **CCR5** for entry, and they are sensitive to specific **inhibitors** of entry via these coreceptors. These observations are relevant to understanding the rapid spread of **HIV**-1 subtype C in the developing world and to the design of intervention and treatment strategies.

L16 ANSWER 19 OF 104 MEDLINE on STN

2003064816. PubMed ID: 12552019. **Human immunodeficiency virus** type 1 attachment, coreceptor, and fusion **inhibitors** are active against both direct and trans infection of primary cells. Ketas Thomas J; Frank Ines; Klasse Per Johan; Sullivan Brian M; Gardner Jason P; Spenlehauer Catherine; Nesin Mirjana; Olson William C; Moore John P; Pope Melissa. (Progenics Pharmaceuticals, Inc., Tarrytown, NY 10591, USA.) Journal of virology, (2003 Feb) 77 (4) 2762-7. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **Inhibitors** of **human immunodeficiency virus** type 1 attachment (CD4-immunoglobulin G subclass 2), **CCR5** usage (PRO 140), and fusion (T-20) were tested on diverse primary cell types that represent the major targets both for infection in vivo and for the **inhibition** of trans infection of target cells by virus bound to dendritic cells. Although minor cell-type-dependent differences in potency were observed, each **inhibitor** was active on each cell type and trans infection was similarly vulnerable to **inhibition** at each stage of the fusion cascade.

L16 ANSWER 20 OF 104 MEDLINE on STN

2002731952. PubMed ID: 12477879. CD4 binding site antibodies **inhibit** **human immunodeficiency virus gp120 envelope** glycoprotein interaction with **CCR5**. Raja Aarti; Venturi Miro; Kwong Peter; Sodroski Joseph. (Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA.) Journal of virology, (2003 Jan) 77 (1) 713-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The **human immunodeficiency virus** type 1 (**HIV**-1) **gp120** exterior glycoprotein is conformationally flexible. Upon binding the host cell receptor, CD4, **gp120** assumes a conformation that is able to bind the **chemokine receptors CCR5** or CXCR4, which act as coreceptors for the virus. CD4-binding-site (CD4BS) antibodies are neutralizing antibodies elicited during natural infection that are directed against **gp120** **epitopes** that overlap the binding site for CD4. Recent studies (S. H. Xiang et al., J. Virol. 76:9888-9899, 2002) suggest that CD4BS antibodies recognize conformations of **gp120** distinct from the CD4-bound conformation. This predicts that the binding of CD4BS antibodies will **inhibit** **chemokine receptor** binding. Here, we show that Fab fragments and complete immunoglobulin molecules of CD4BS antibodies **inhibit** CD4-independent **gp120** binding to **CCR5** and cell-cell fusion mediated by CD4-independent **HIV**-1 **envelope** glycoproteins. These results are consistent with a model in which the binding of CD4BS antibodies limits the ability of **gp120** to assume a conformation required for coreceptor binding.

L16 ANSWER 21 OF 104 MEDLINE on STN

2002726677. PubMed ID: 12444251. Sensitivity of **HIV**-1 to entry **inhibitors** correlates with **envelope**/coreceptor affinity, receptor density, and fusion kinetics. Reeves Jacqueline D; Gallo Stephen A; Ahmad Navid; Miamidian John L; Harvey Phoebe E; Sharron Matthew; Pohlmann Stefan; Sfakianos Jeffrey N; Derdeyn Cynthia A; Blumenthal Robert; Hunter Eric; Doms Robert W. (Department of Microbiology, University of Pennsylvania, 225 Johnson Pavilion, 3610 Hamilton Walk, Philadelphia, PA 19104, USA.. jreeves@mail.med.upenn.edu) . Proceedings of the National Academy of Sciences of the United States of America, (2002 Dec 10) 99 (25) 16249-54. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB **HIV** entry **inhibitors** include coreceptor antagonists and the fusion **inhibitor** T-20. T-20 binds the first helical region (HR1) in the gp41 subunit of the viral **envelope** (**Env**) protein and prevents conformational changes required for membrane fusion. HR1 appears to become accessible to T-20 after **Env** binds CD4, whereas coreceptor binding is thought to induce the final conformational changes that lead to membrane fusion. Thus, T-20 binds to a structural intermediate of the fusion process. Primary viruses exhibit considerable variability in T-20 sensitivity, and determinants outside of HR1 can affect sensitivity by unknown mechanisms. We studied chimeric **Env** proteins containing different V3 loop sequences and found that gp120coreceptor affinity correlated with T-20 and coreceptor antagonist sensitivity, with greater affinity resulting in increased resistance to both classes of entry **inhibitors**. Enhanced affinity resulted in more rapid fusion kinetics, reducing the time during which **Env** is sensitive to T-20. Reduced coreceptor expression levels also delayed fusion kinetics and enhanced virus sensitivity to T-20, whereas increased coreceptor levels had the opposite effect. A single amino acid change (K421D) in the bridging sheet region of the primary virus strain YU2 reduced affinity for **CCR5** and increased T-20 sensitivity by about 30-fold. Thus, mutations in **Env** that affect receptor engagement and membrane fusion rates can alter entry **inhibitor** sensitivity. Because coreceptor expression levels are typically limiting in vivo, individuals who express lower coreceptor levels may respond more favorably to entry **inhibitors** such as T-20, whose effectiveness we show depends in part on fusion kinetics.

L16 ANSWER 22 OF 104 MEDLINE on STN

2002725262. PubMed ID: 12487827. Characterization of CD4-induced **epitopes** on the **HIV** type 1 **gp120** **envelope** glycoprotein recognized

By neutralizing human monoclonal antibodies. Xiang Shi Hua; Boka Najah; Choudhary Rabeea K; Sodroski Joseph; Robinson James E. (Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, USA.) AIDS research and human retroviruses, (2002 Nov 1) 18 (16) 1207-17. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB The entry of **human immunodeficiency virus** (**HIV**-1) into target cells typically requires the sequential binding of the viral exterior **envelope** glycoprotein, **gp120**, to CD4 and a **chemokine receptor**. CD4 binding exposes **gp120 epitopes** recognized by CD4-induced (CD4i) antibodies, which can block virus binding to the **chemokine receptor**. We identified three new CD4i antibodies from an **HIV**-1-infected individual and localized their **epitopes**. These **epitopes** include a highly conserved **gp120** beta-strand encompassing residues 419-424, which is also important for binding to the **CCR5 chemokine receptor**. All of the CD4i antibodies **inhibited** the binding of **gp120**-CD4 complexes to **CCR5**. CD4i antibodies and CD4 reciprocally induced each other's binding, suggesting that these ligands recognize a similar **gp120** conformation. The CD4i antibodies neutralized laboratory-adapted **HIV**-1 isolates; primary isolates were more resistant to neutralization by these antibodies. Thus, all known CD4i antibodies recognize a common, conserved **gp120** element overlapping the binding site for the **CCR5 chemokine receptor**.

L16 ANSWER 23 OF 104 MEDLINE on STN

2002701461. PubMed ID: 12462149. Evaluation of current approaches to **inhibit HIV** entry. Pohlmann S; Doms R W. (Department of Microbiology, University of Pennsylvania, Philadelphia, PA 19104, USA.) Current drug targets. Infectious disorders, (2002 Mar) 2 (1) 9-16. Ref: 111. Journal code: 101128002. ISSN: 1568-0053. Pub. country: Netherlands. Language: English.

AB Highly active **inhibitors** of **human immunodeficiency virus** (**HIV**) reverse transcriptase and protease have made it possible to dramatically reduce virus load in **HIV**-positive individuals. However, the presence of viral reservoirs, the emergence of drug-resistant **HIV** variants and the side effects of these compounds call for research into new drugs that target different stages of the viral life cycle. One attractive target is the first step in **HIV** replication: entry of virus into cells. **HIV** entry is initiated by the attachment of the virus to the host cell membrane, which is some cases involves binding to attachment factors such as DC-SIGN. Subsequent interaction of the **envelope** protein (**Env**) with the CD4 receptor causes conformational changes that enable **Env** to interact with a coreceptor, generally the **chemokine receptors CCR5** or CXCR4. Coreceptor engagement triggers the final conformational changes in **Env**, which mediate lipid mixing between the viral and cellular membranes. All of these steps are potential targets for therapeutic intervention: targeting proteins that mediate viral attachment may reduce **HIV** transmission, while receptor blockade will **inhibit** virus entry. Highly conserved domains in **Env** which bind to CD4 and coreceptor are promising targets for broadly neutralizing antibodies, and **peptide inhibitors** that bind to **Env** and that block membrane fusion are in advanced clinical trials. These new approaches may supplement current **HIV** therapy and may assist in the development of an **HIV** vaccine.

L16 ANSWER 24 OF 104 MEDLINE on STN

2002649635. PubMed ID: 12408990. Ionic interaction of the **HIV**-1 V3 domain with **CCR5** and deregulation of T lymphocyte function. Baritaki Stavroula; Zafiropoulos Alexis; Sioumpara Maria; Politis Manolis; Spandidos Demetrios A; Krambovitis Elias. (Department of Applied Biochemistry and Immunology, Institute of Molecular Biology and Biotechnology, Vassilika Vouton, Heraklion, Crete, Greece.) Biochemical and biophysical research communications, (2002 Nov 8) 298 (4) 574-80. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB We have reported that the principal neutralizing domain of V3 of the **HIV**-1 **gp120** induces an antigen-specific activation apoptosis of

responding effector CD4+ T lymphocytes, a phenomenon **inhibited** by RANTES, an agonist of **CCR5**. Here, addressing the question of how a hypervariable region could induce such a selective reaction, we demonstrated that the magnitude of the activation phase was dependent on the number of basic amino acids present in the V3 **peptide**, an observation confirmed by using V3 **peptides** with appropriate basic amino acid substitutions. The relative position of the amino acids in the V3 **peptide** did not affect the biological phenomenon. Using surface plasmon resonance biosensor analysis, we also provided direct evidence of the influence of basic amino acids in the interaction between V3 and the amino terminal domain of **CCR5**. Sulphation of tyrosines in the **CCR5** **peptide** was essential. Our results confirm **gp120** modelling predictions and demonstrate simple molecular ionic interactions as capable of affecting key cell events, the wider biological implications of which need to be further explored.

L16 ANSWER 25 OF 104 MEDLINE on STN

2002646749. PubMed ID: 12406507. A post-CD4-binding step involving interaction of the V3 region of viral **gp120** with host cell surface glycosphingolipids is common to entry and infection by diverse **HIV**-1 strains. Nehete Pramod N; Vela Eric M; Hossain M M; Sarkar Asis K; Yahi Nouara; Fantini Jacques; Sastry K Jagannadha. (Department of Veterinary Sciences, The University of Texas M.D. Anderson Cancer Center, Science Park, 650 Cool Water Drive, Bastrop 78602, USA.) Antiviral research, (2002 Dec) 56 (3) 233-51. Journal code: 8109699. ISSN: 0166-3542. Pub. country: Netherlands. Language: English.

AB The V3-loop region in the **envelope** protein **gp120** of **HIV** is critical for viral infection, but its interaction with the target cells is not clear. Using synthetic **peptides**, representing linear V3 sequences as reagents, we obtained evidence to show **inhibition** of infection by both T-cell- and macrophage-tropic strains of **human immunodeficiency virus** type 1 (**HIV**-1) (X4 and R5, respectively), without interfering with **gp120**-CD4 interaction, by the V3 **peptides** through binding to host cell membrane glycosphingolipids (GSL). Synthetic **peptides** mimicking the central 15-21 amino acid sequence of the V3-loop region in both X4 and R5 strains of **HIV**-1 competed with and blocked the entry of both types of **HIV** isolates. These **HIV-inhibitory** V3 **peptides** exhibited specific binding to target cells that was not competed by antibodies to either the primary receptor CD4 or the co-receptors CXCR-4 and **CCR5**. However, R15K, the V3 **peptide** from **HIV**-1 IIIB **gp120** exhibited specific binding to three distinct cell surface GSL: GM3, Gb3, and GalCer. Further, R15K **inhibited** GSL binding of **gp120** from both **HIV**-1 IIIB (X4, Gb3-binding strain) and **HIV**-1 89.6 (X4R5, GM3-binding strain). Together, these results suggest a critical V3-mediated post-CD4-binding event involving cell surface GSL binding represented by the **HIV-inhibitory** V3 **peptides**, that is common for the entry of diverse **HIV**-1 strains and may be targeted for the development of novel **HIV** therapeutics aimed at blocking viral entry.

L16 ANSWER 26 OF 104 MEDLINE on STN

2002636821. PubMed ID: 12396109. Synthetic **peptides** for study of **human immunodeficiency virus** infection. Dettin Monica; Scarinci Claudia; Pasquato Antonella; Di Bello Carlo. (Department of Chemical Process Engineering, University of Padova, Italy.) Applied biochemistry and biotechnology, (2002 Jul-Dec) 102-103 (1-6) 41-7. Ref: 18. Journal code: 8208561. ISSN: 0273-2289. Pub. country: United States. Language: English.

AB The formation of a complex among **gp120**, CD4, and **CCR5**/CXCR4 represents a key step in **human immunodeficiency virus** (**HIV**) infection. The use of synthetic **peptides** reproducing sequences of these surface proteins has increased knowledge about the interactions that determine the penetration of **HIV** viruses into target cells. The final aim of such investigations is the design of molecules able to **inhibit** the initial step of infection and the development of high-sensitivity in vitro assays for detection of **HIV**. In particular, the studies presented herein concern the role of the **gp120** V3 loop in the CD4 binding, the importance of the N-terminal sequence of **HIV**-coreceptor **CCR5**, the sequences

patterned on CXCR4 natural ligand (stromal derived factor 1 [SDF-1]) as **inhibitory peptides**, and the importance of substrate secondary structure in determining the enzymatic processing of **gp120** precursor (**gp160**).

L16 ANSWER 27 OF 104 MEDLINE on STN

2002611442. PubMed ID: 12368305. Engineered CD4- and CXCR4-using simian immunodeficiency virus from African green monkeys is neutralization sensitive and replicates in nonstimulated lymphocytes. Konig Renate R; Flory Egbert; Steidl Stefanie; Neumann Jeanette; Coulibaly Cheick; Holznagel Edgar; Holzammer Silke; Norley Stephen; Cichutek Klaus. (Department of Medical Biotechnology, Paul-Ehrlich-Institut, 63225 Langen, Germany.) Journal of virology, (2002 Nov) 76 (21) 10627-36. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB During **human immunodeficiency virus** type 1 (**HIV**-1) infection, disease progression correlates with the occurrence of variants using the coreceptor CXCR4 for cell entry. In contrast, apathogenic simian immunodeficiency virus (SIV) from African green monkeys (SIVagm), specifically the molecular virus clone SIVagm3mc, uses **CCR5**, Bob, and Bonzo as coreceptors throughout the course of infection. The influence of an altered coreceptor usage on SIVagm3mc replication was studied in vitro and in vivo. The putative coreceptor binding domain, the V3 region of the surface **envelope** (SU) glycoprotein, was replaced by the V3 loop of a CD4- and CXCR4-tropic **HIV**-1 strain. The resulting virus, termed SIVagm3-X4mc, exclusively used CD4 and CXCR4 for cell entry. Consequently, its in vitro replication was **inhibited** by SDF-1, the natural ligand of CXCR4. Surprisingly, SIVagm3-X4mc was able to replicate in vitro not only in interleukin-2- and phytohemagglutinin-stimulated but also in nonstimulated peripheral blood mononuclear cells (PBMCs) from nonhuman primates. After experimental infection of two pig-tailed macaques with either SIVagm3-X4mc or SIVagm3mc, the coreceptor usage was maintained during in vivo replication. Cell-associated and plasma viral loads, as well as viral DNA copy numbers, were found to be comparable between SIVagm3mc and SIVagm 3-X4mc infections, and no pathological changes were observed up to 14 months postinfection. Interestingly, the V3 loop exchange rendered SIVagm3-X4mc susceptible to neutralizing antibodies present in the sera of SIVagm3-X4mc- and SIVagm3mc-infected pig-tailed macaques. Our study describes for the first time a successful exchange of a V3 loop in nonpathogenic SIVagm resulting in CD4 and CXCR4 usage and modulation of virus replication in nonstimulated PBMCs as well as sensitivity toward neutralization.

L16 ANSWER 28 OF 104 MEDLINE on STN

2002490331. PubMed ID: 12351957. Evolution of the gp41 **env** region in **HIV**-infected patients receiving T-20, a fusion **inhibitor**. Poveda Eva; Rodes Berta; Toro Carlos; Martin-Carbonero Luz; Gonzalez-Lahoz Juan; Soriano Vincent. (Department of Infectious Diseases, Hospital Carlos Ill, Instituto de Salud Carlos Ill, Madrid, Spain.) AIDS (London, England), (2002 Sep 27) 16 (14) 1959-61. Journal code: 8710219. ISSN: 0269-9370. Pub. country: England: United Kingdom. Language: English.

L16 ANSWER 29 OF 104 MEDLINE on STN

2002423430. PubMed ID: 12103434. Characterization of the anti-**HIV** effects of native lactoferrin and other milk proteins and protein-derived **peptides**. Berkhout Ben; van Wamel Jeroen L B; Beljaars Leonie; Meijer Dirk K F; Visser Servaas; Floris Rene. (Department of Human Retrovirology, Academic Medical Center, University of Amsterdam, Meibergdreef 15, 1105 AZ, Amsterdam, The Netherlands.. b.berkhout@amc.uva.nl) . Antiviral research, (2002 Aug) 55 (2) 341-55. Journal code: 8109699. ISSN: 0166-3542. Pub. country: Netherlands. Language: English.

AB In a search for natural proteins with anti-**HIV** activity, we screened a large set of purified proteins from bovine milk and **peptide** fragments thereof. Because several charged proteins and **peptides** are known to **inhibit** the process of virus entry, we selected proteins with an unusual charge composition or hydrophobicity profile. In contrast with some

chemically modified (strongly negative) milk proteins, unmodified alpha(s2)-, beta- and kappa-casein, as well as several negatively and positively charged fragments thereof, did not show significant **inhibition** of virus replication. In fact, **HIV**-1 replication was elevated in the presence of beta-casein or amphiphilic fragments thereof. Bovine lactoferrin (bLF), a milk protein of 80 kDa, showed considerable **inhibitory** activity against **HIV**-1 with an IC50 of 0.4 microM. Modest **inhibition** was obtained with lactoferricin, a highly positively charged loop domain of bLF, indicating that other domains within the native bLF protein may also be required for **inhibition**. bLF blocked **HIV**-1 variants that use either the CXCR4 or the **CCR5** coreceptor. In order to obtain further insight into the mechanism of action of this **antiviral** protein, we selected a bLF-resistant **HIV**-1 variant. The bLF-resistance phenotype is mediated by the viral **envelope** protein, which contains two interesting mutations that have previously been associated with an altered virus-host interaction and a modified receptor-coreceptor interaction. These results demonstrate that bLF targets the **HIV**-1 entry process.

L16 ANSWER 30 OF 104 MEDLINE on STN

2002421227. PubMed ID: 12176010. Human alpha-fetoprotein binds to primary macrophages. Atemezem Aurelie; Mbemba Elisabeth; Marfaing Renee; Vaysse Jenny; Pontet Michel; Saffar Line; Charnaux Nathalie; Gattegno Liliane. (UPRES 3410, Biotherapies, Benefices et Risques, UFR-SMBH, Universite Paris XIII, Bobigny et Hopital Jean Verdier, Bondy 93017, France.) Biochemical and biophysical research communications, (2002 Aug 23) 296 (3) 507-14. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB We have previously reported that alpha-fetoprotein (AFP) **inhibits** infection of human monocyte-derived macrophages (MDM) by R5-**HIV**-1 strains and that a **peptide** mimicking the clade B **HIV**-1 **gp120** consensus V3 domain (V3Cs) binds to **CCR5**. We demonstrate here that AFP binds high- and low-affinity binding sites of MDM, characterized, respectively, by 5.15 and 100nM K(d) values. Heat denaturation or neuraminidase treatment of AFP **inhibits** this binding, suggesting the involvement of protein-protein and lectin-carbohydrate interactions. Moreover, AFP displaces V3Cs binding to MDM. In addition, MIP-1beta, the most specific **CCR5** ligand, displaces AFP binding to MDM (IC(50)=4.3nM). Finally, we demonstrate that AFP binds to a ligand of **HIV**-**gp120** V3Cs domain, **CCR5**, expressed by MDM and by HeLa cells expressing **CCR5**. Such binding is not observed in the presence of HeLa cells lacking **CCR5**. The present results provide strong evidence that AFP directly binds to **CCR5** expressed by human primary macrophages and by transfected **CCR5**+ HeLa cells.

L16 ANSWER 31 OF 104 MEDLINE on STN

2002375440. PubMed ID: 12120995. **HIV** receptors and cellular tropism. Weiss Robin A. (Department of Immunology and Molecular Pathology, University College London, United Kingdom.. r.weiss@ucl.ac.uk) . IUBMB life, (2002 Apr-May) 53 (4-5) 201-5. Ref: 27. Journal code: 100888706. ISSN: 1521-6543. Pub. country: England: United Kingdom. Language: English.

AB Viruses use specific cell surface receptors to bind to and subsequently gain entry into their host cells. Some retroviruses such as **HIV**-1 and **HIV**-2 utilize one receptor for high-affinity binding (CD4), and a separate coreceptor to mediate fusion of the viral **envelope** with the cell membrane (**CCR5** or CXCR4). The identification of these receptors explains the cellular tropism of **HIV**, and hence its pathogenesis leading to immune deficiency (T-helper cell depletion), the wasting syndrome (macrophage infection), and dementia (microglia infection). **HIV** can infect cells by membrane fusion at the cell surface and by receptor-mediated endocytosis. Knowledge of the **HIV** receptors has led to practical developments such as **inhibitory** drugs, reasons for genetic resistance to infection, and should inform the judicious choice of candidate vaccines.

L16 ANSWER 32 OF 104 MEDLINE on STN

2002344926. PubMed ID: 12072497. Coreceptor phenotype of natural **human immunodeficiency virus** with nef deleted evolves in vivo, leading to increased virulence. Jekle Andreas; Schramm Birgit; Jayakumar Prerana; Trautner Verena; Schols Dominique; De Clercq Erik; Mills John; Crowe Suzanne M; Goldsmith Mark A. (Gladstone Institute of Virology and Immunology, San Francisco, CA 94141-9100, USA.) Journal of virology, (2002 Jul) 76 (14) 6966-73. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The Sydney Blood Bank Cohort is a group of patients with slowly progressive infection by a **human immunodeficiency virus** strain containing spontaneous deletions within the nef long terminal repeat region. In 1999, 18 years after the initial infection, one of the members (D36) developed AIDS. In this work, we used an ex vivo human lymphoid cell culture system to analyze two viral isolates obtained from this patient, one prior to the onset of AIDS in 1995 and one after disease progression in 1999. Both D36 isolates were less potent in depleting CD4(+) T cells than a reference dualtropic, nef-bearing viral isolate. However, the 1999 isolate was measurably more cytotoxic to CD4(+) T cells than the 1995 isolate. Interestingly, although both isolates were nearly equally potent in depleting **CCR5**(+) CD4(+) T cells, the cytotoxic effect of the 1999 isolate toward **CCR5**(-) CD4(+) T cells was significantly higher. Furthermore, GHOST cell infection assays and blocking experiments with the CXCR4 **inhibitor** AMD3100 showed that the later D36 1999 isolate could infect both **CCR5**(+) and **CCR5**(-) CXCR4(+) cells efficiently, while infection by the 1995 isolate was nearly completely restricted to **CCR5**(+) cells. Sequence analysis of the V1/V2 and V3 regions of the viral **envelope** protein **gp120** revealed that the more efficient CXCR4 usage of the later isolate might be caused by an additional potential N-glycosylation site in the V1/V2 loop. In conclusion, these data show that an in vivo evolution of the tropism of this nef-deleted strain toward an X4 phenotype was associated with a higher cytopathic potential and progression to AIDS.

L16 ANSWER 33 OF 104 MEDLINE on STN

2002284809. PubMed ID: 11997472. Broadly cross-reactive **HIV**-1-neutralizing human monoclonal Fab selected for binding to **gp120**-CD4-**CCR5** complexes. Moulard Maxime; Phogat Sanjay K; Shu Yuuei; Labrijn Aran F; Xiao Xiaodong; Binley James M; Zhang Mei-Yun; Sidorov Igor A; Broder Christopher C; Robinson James; Parren Paul W H I; Burton Dennis R; Dimitrov Dimiter S. (Department of Immunology, The Scripps Research Institute, La Jolla, CA 92037, USA.) Proceedings of the National Academy of Sciences of the United States of America, (2002 May 14) 99 (10) 6913-8. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB **HIV**-1 entry into cells involves formation of a complex between **gp120** of the viral **envelope** glycoprotein (**Env**), a receptor (CD4), and a coreceptor, typically **CCR5**. Here we provide evidence that purified **gp120**(JR-FL)-CD4-**CCR5** complexes exhibit an **epitope** recognized by a Fab (X5) obtained by selection of a phage display library from a seropositive donor with a relatively high broadly neutralizing serum antibody titer against an immobilized form of the trimolecular complex. X5 bound with high (nM) affinity to a variety of **Envs**, including primary isolates from different clades and **Envs** with deleted variable loops (V1, -2, -3). Its binding was significantly increased by CD4 and slightly enhanced by **CCR5**. X5 **inhibited** infection of peripheral blood mononuclear cells by a selection of representative **HIV**-1 primary isolates from clades A, B, C, D, E, F, and G with an efficiency comparable to that of the broadly neutralizing antibody IgG1 b12. Furthermore, X5 **inhibited** cell fusion mediated by **Envs** from R5, X4, and R5X4 viruses. Of the five broadly cross-reactive **HIV**-1-neutralizing human monoclonal antibodies known to date, X5 is the only one that exhibits increased binding to **gp120** complexed with receptors. These findings suggest that X5 could possibly be used as entry **inhibitor** alone or in combination with other **antiretroviral** drugs for the treatment of **HIV**-1-infected individuals, provide evidence for the existence of conserved receptor-inducible **gp120 epitopes** that can serve as targets for potent

broadly cross reactive neutralizing antibodies in **HIV** 1 infected patients, and have important conceptual and practical implications for the development of vaccines and **inhibitors**.

L16 ANSWER 34 OF 104 MEDLINE on STN

2002269478. PubMed ID: 12009872. Inter-retroviral fusion mediated by **human immunodeficiency virus** or murine leukemia virus glycoproteins: independence of cellular membranes and membrane vesicles. Sparacio Sandra; Pfeiffer Tanya; Holtkotte Denise; Bosch Valerie. (Forschungsschwerpunkt Angewandte Tumorvirologie, F0200, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 242, Heidelberg, D-69120, Germany.) Virology, (2002 Mar 15) 294 (2) 305-11. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB We have recently demonstrated for the first time that inter-retroviral membrane fusion, i.e., membrane fusion between individual retroviral particle populations with incorporated **HIV**-1 **Env** and cellular receptors, respectively, can occur (Sparacio et al. 2000, Virology 271: 248-252). We have extended these analyses here and confirmed that fusion between particles can occur in the extracellular medium independent of any cellular membranes and that luciferase transduction, mediated by the fused structures, is independent of significant potential contribution by contaminating membrane vesicles. We have additionally analyzed whether membrane fusion between **HIV**-like particles can be mediated by amphotropic murine leukemia virus (MuLV) glycoprotein and its respective cellular receptor, PiT-2. We demonstrate that PiT-2 can be incorporated into **HIV**-like particles and can fuse with MuLV-**Env**-carrying particles. This occurs only in the situation in which the incorporated MuLV-**Env** protein has been activated to fusion activity by **HIV** protease-mediated removal of the C-terminal R-**peptide** and is completely **inhibited** when the respective particles are generated in the presence of the **HIV** protease **inhibitor**, Saquinavir.

L16 ANSWER 35 OF 104 MEDLINE on STN

2002221502. PubMed ID: 11958688. Virologic risk factors for vertical transmission of **HIV** type 1 in Puerto Rico. Arroyo M A; Tien H; Pagan M; Swanstrom R; Hillyer G V; Cadilla C L; Melendez-Guerrero L M. (Department of Microbiology and Medical Zoology, University of Puerto Rico, School of Medicine, San Juan, Puerto Rico 00936.) AIDS research and human retroviruses, (2002 Apr 10) 18 (6) 447-60. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB **HIV**-1 vertical transmission in Puerto Rico has decreased significantly due to the implementation of **antiviral** therapy. Several studies have shown that the phenotype of the **HIV**-1 isolates initially recovered from infected infants has generally been one that replicates rapidly, infects macrophages, and preferentially use the **CCR5** coreceptor. Our hypothesis is that viral genotypic and phenotypic differences exist between **HIV**-1 nontransmitter and transmitter mothers. Viral DNA samples and virus isolates were analyzed from a Puerto Rican perinatal population. Heteroduplex tracking assay (HTA) was performed on DNA samples to detect **env** V3 evolutionary variants and the extent of heterogeneity within each sample. **HIV**-1 C2-V3 variants were cloned from each patient to study sequence variation among the groups. Differences in replication kinetics of viral isolates in macrophage and GHOST **CCR5** cells were analyzed by use of repeated measures linear regression analysis. HTA analysis showed that only two nontransmitter patient samples showed the presence of evolutionary variants. Phylogenetic analysis between maternal-infant pairs showed that transmission of a single maternal variant occurred, with the exception of one sample pair. When evaluating amino acid sequences from cloned PCR products, nontransmitting mothers appear to have a higher number of distinct sequences than both the transmitting mothers ($p = 0.0410$) and the infected infants ($p = 0.0315$). Analysis of replication kinetics indicated that transmitters showed faster replication kinetics in GHOST **CCR5** cell cultures at 12 days postinfection ($p = 0.0434$) and 15 days postinfection ($p = 0.0181$). In conclusion, viral homogeneity and rapid replication kinetics were correlated with vertical transmission.

L16 ANSWER 36 OF 104 MEDLINE on STN
2002203382. PubMed ID: 11936872. Characterization of **HIV** isolates from Puerto Rican maternal-infant pairs reveal predominance of non-syncytium inducing (NSI) variants with **CCR5** genotype. Melendez-Guerrero L M; Arroyo M A; Vega M E; Jimenez E; Hillyer G V; Cadilla C L. (Department of Microbiology and Medical Zoology, University of Puerto Rico School of Medicine, San Juan 00936-5067, USA.. lmelendez@rcm.upr.edu) . Cellular and molecular biology (Noisy-le-Grand, France), (2001) 47 Online Pub OL39-47. Journal code: 9216789. ISSN: 0145-5680. Pub. country: France. Language: English.

AB In this study, **HIV**-1 variants from a cohort of forty-eight Puerto Rican pregnant women and their 50 infants (one had triplets), were isolated and characterized, in order to determine the type of **HIV**-1 variants that are predominantly transmitted. All were enrolled in the prenatal AIDS Clinical Trials Group (ACTG) and received anti-retroviral therapy. Fifteen of the 50 infants (30%) were positive by V3 PCR suggesting that they harbored a copy of the **HIV envelope** gene. Three of 50 infants (6%) were **HIV**-1 culture and PCR positive, indicating active infection. **HIV**-positive cultures were obtained from 32 of the 48 mothers. Sixty two percent of the isolates (20/32) were macrophage-tropic and non-syncytium inducing, three percent (1/32) had dual tropism, and thirty four percent (11/32) were non-syncytium inducing and did not grow in macrophages. Phenotype and genotype of the **HIV** variants from the three infected infants revealed the presence of macrophage-tropic and non-syncytium-inducing strains. Genotype analysis of the **HIV env** V3 loop revealed the presence of specific amino acids that are predictive of **CCR5** usage. Sequence analysis of the **HIV** pol gene from the three infected infants indicated that vertical transmission was not caused by the presence of **antiviral** resistance mutations. These results indicate that mothers undergoing **antiretroviral** treatment at different stages of the disease and with different viral loads transmit predominantly macrophage-tropic/non-syncytium inducing/**CCR5** variants to their infants.

L16 ANSWER 37 OF 104 MEDLINE on STN
2002194788. PubMed ID: 11926873. Researchers explore new anti-**HIV** agents. Stephenson Joan. JAMA : journal of the American Medical Association, (2002 Apr 3) 287 (13) 1635-7. Journal code: 7501160. ISSN: 0098-7484. Pub. country: United States. Language: English.

L16 ANSWER 38 OF 104 MEDLINE on STN
2002164774. PubMed ID: 11854425. Multiple active states and oligomerization of **CCR5** revealed by functional properties of monoclonal antibodies. Blanpain Cedric; Vanderwinden Jean-Marie; Cihak Josef; Wittamer Valerie; Le Poul Emmanuel; Issafras Hassan; Stangassinger Manfred; Vassart Gilbert; Marullo Stefano; Schlndorff Detlef; Parmentier Marc; Mack Matthias. (Institut de Recherche Interdisciplinaire en Biologie Humaine et Nucleaire, Universite Libre de Bruxelles, B-1070 Brussels, Belgium.) Molecular biology of the cell, (2002 Feb) 13 (2) 723-37. Journal code: 9201390. ISSN: 1059-1524. Pub. country: United States. Language: English.

AB CC-**chemokine receptor** 5 (**CCR5**) is the principal coreceptor for macrophage-tropic strains of **human immunodeficiency virus** type 1 (**HIV**-1). We have generated a set of anti-**CCR5** monoclonal antibodies and characterized them in terms of **epitope** recognition, competition with chemokine binding, receptor activation and trafficking, and coreceptor activity. MC-4, MC-5, and MC-7 mapped to the amino-terminal domain, MC-1 to the second extracellular loop, and MC-6 to a conformational **epitope** covering multiple extracellular domains. MC-1 and MC-6 **inhibited** regulated on activation normal T cell expressed and secreted (RANTES), macrophage inflammatory **polypeptide**-1beta, and **Env** binding, whereas MC-5 **inhibited** macrophage inflammatory **polypeptide**-1beta and **Env** but not RANTES binding. MC-6 induced signaling in different functional assays, suggesting that this monoclonal antibody stabilizes an active conformation of **CCR5**. Flow cytometry and real-time confocal microscopy showed that MC-1 promoted strong **CCR5** endocytosis. MC-1 but not its monovalent isoforms induced an increase in the transfer of energy between

CCR5 molecules. Also, its monovalent isoforms bound efficiently, but did not internalize the receptor. In contrast, MC-4 did not prevent RANTES binding or subsequent signaling, but **inhibited** its ability to promote **CCR5** internalization. These results suggest the existence of multiple active conformations of **CCR5** and indicate that **CCR5** oligomers are involved in an internalization process that is distinct from that induced by the receptor's agonists.

L16 ANSWER 39 OF 104 MEDLINE on STN

2002140279. PubMed ID: 11821899. Primary intestinal epithelial cells selectively transfer R5 **HIV**-1 to **CCR5**+ cells. Meng Gang; Wei Xiping; Wu Xiaoyun; Sellers Marty T; Decker Julie M; Moldoveanu Zina; Orenstein Jan M; Graham Martin F; Kappes John C; Mestecky Jiri; Shaw George M; Smith Phillip D. (Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA.) Nature medicine, (2002 Feb) 8 (2) 150-6. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB The upper gastrointestinal tract is a principal route of **HIV**-1 entry in vertical transmission and after oral-genital contact. The phenotype of the newly acquired virus is predominantly R5 (**CCR5**-tropic) and not X4 (CXCR4-tropic), although both R5 and X4 viruses are frequently inoculated onto the mucosa. Here we show that primary intestinal (jejunal) epithelial cells express galactosylceramide, an alternative primary receptor for **HIV**-1, and **CCR5** but not CXCR4. Moreover, we show that intestinal epithelial cells transfer R5, but not X4, viruses to **CCR5**+ indicator cells, which can efficiently replicate and amplify virus expression. Transfer was remarkably efficient and was not **inhibited** by the fusion blocker T-20, but was substantially reduced by colchicine and low (4 degrees C) temperature, suggesting endocytotic uptake and microtubule-dependent transcytosis of **HIV**-1. Our finding that **CCR5**+ intestinal epithelial cells select and transfer exclusively R5 viruses indicates a mechanism for the selective transmission of R5 **HIV**-1 in primary infection acquired through the upper gastrointestinal tract.

L16 ANSWER 40 OF 104 MEDLINE on STN

2002064292. PubMed ID: 11789660. Receptors for chemotactic formyl **peptides** as pharmacological targets. Le Yingying; Yang Yiming; Cui Youhong; Yazawa Hiroshi; Gong Wanghua; Qiu Cunping; Wang Ji Ming. (Laboratory of Molecular Immunoregulation, Center for Cancer Research, National Cancer Institute at Frederick, MD 21702, USA.. ley@mail.ncifcrf.gov) . International immunopharmacology, (2002 Jan) 2 (1) 1-13. Ref: 112. Journal code: 100965259. ISSN: 1567-5769. Pub. country: Netherlands. Language: English.

AB Leukocytes accumulate at sites of inflammation and immunological reaction in response to locally existing chemotactic mediators. N-formyl **peptides**, such as fMet-Leu-Phe (fMLF), are some of the first identified and most potent chemoattractants for phagocytic leukocytes. In addition to the bacterial **peptide** fMLF and the putative endogenously produced formylated **peptides**, a number of novel **peptide** agonists have recently been identified that selectively activate the high-affinity fMLF receptor FPR and/or its low-affinity variant FPRL1, both of which belong to the seven-transmembrane (STM), G protein-coupled receptor (GPCR) superfamily. These agonists include **peptide** domains derived from the **envelope** proteins of **human immunodeficiency virus** type 1 (**HIV**-1) and at least three amyloidogenic **polypeptides**, the human acute phase protein serum amyloid A, the 42 amino acid form of beta amyloid **peptide** and a 21 amino acid fragment of human prion. Furthermore, a cleavage fragment of neutrophil granule-derived bactericidal cathelicidin, LL-37, is also a chemotactic agonist for FPRL1. Activation of formyl **peptide** receptors results in increased cell migration, phagocytosis, release of proinflammatory mediators, and the signaling cascade culminates in heterologous desensitization of other STM receptors including **chemokine receptors CCR5** and CXCR4, two coreceptors for **HIV**-1. Thus, by interacting with a variety of exogenous and host-derived agonists, formyl **peptide** receptors may play important roles in proinflammatory and immunological diseases and constitute a novel group of pharmacological

targets.

L16 ANSWER 41 OF 104 MEDLINE on STN

2002046650. PubMed ID: 11752155. A variable region 3 (V3) mutation determines a global neutralization phenotype and CD4-independent infectivity of a **human immunodeficiency virus** type 1 **envelope** associated with a broadly cross-reactive, primary virus-neutralizing antibody response. Zhang Peng Fei; Bouma Peter; Park Eun Ju; Margolick Joseph B; Robinson James E; Zolla-Pazner Susan; Flora Michael N; Quinnan Gerald V Jr. (Department of Preventive Medicine and Biometrics, Biomedical Instrumentation Center, Uniformed Services University of the Health Sciences, Bethesda 20814, USA.) Journal of virology, (2002 Jan) 76 (2) 644-55. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The human serum **human immunodeficiency virus** type 1 (**HIV**-1)-neutralizing serum 2 (HNS2) neutralizes many primary isolates of different clades of **HIV**-1, and virus expressing **envelope** from the same donor, clone R2, is neutralized cross-reactively by **HIV**-immune human sera. The basis for this cross-reactivity was investigated. It was found that a rare mutation in the proximal limb of variable region 3 (V3), 313-4 PM, caused virus pseudotyped with the R2 **envelope** to be highly sensitive to neutralization by monoclonal antibodies (MAbs) directed against conformation-sensitive **epitopes** at the tip of the V3 loop, such as 19b, and moderately sensitive to MAbs against CD4 binding site (CD4bs) and CD4-induced (CD4i) **epitopes**, soluble CD4 (sCD4), and HNS2. In addition, introduction of this sequence by mutagenesis caused enhanced sensitivity to neutralization by 19b, anti-CD4i MAb, and HNS2 in three other primary **HIV**-1 **envelopes** and by anti-CD4bs MAb and sCD4 in one of the three. The 313-4 PM sequence also conferred increased infectivity for CD4(+) **CCR5**(+) cells and the ability to infect **CCR5**(+) cells upon all of these four and two of these four **HIV**-1 **envelopes**, respectively. Neutralization of R2 by HNS2 was substantially **inhibited** by the cyclized R2 V3 35-mer synthetic **peptide**. Similarly, the **peptide** also had some lesser efficacy in blocking neutralization of R2 by other sera or of neutralization of other primary viruses by HNS2. Together, these results indicate that the unusual V3 mutation in the R2 clone accounts for its uncommon neutralization sensitivity phenotype and its capacity to mediate CD4-independent infection, both of which could relate to immunogenicity and the neutralizing activity of HNS2. This is also the first primary **HIV**-1 isolate **envelope** glycoprotein found to be competent for CD4-independent infection.

L16 ANSWER 42 OF 104 MEDLINE on STN

2001674068. PubMed ID: 11562282. New developments in anti-**HIV** chemotherapy. De Clercq E. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium.. erik.declercq@rega.kuleuven.ac.be) . Current medicinal chemistry, (2001 Nov) 8 (13) 1543-72. Ref: 228. Journal code: 9440157. ISSN: 0929-8673. Pub. country: Netherlands. Language: English.

AB Virtually all the compounds that are currently used, or under advanced clinical trial, for the treatment of **HIV** infections, belong to one of the following classes: (i) nucleoside/nucleotide reverse transcriptase **inhibitors** (NRTIs): i.e., zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir (ABC), emtricitabine [(-)FTC], tenofovir (PMPA) disoproxil fumarate; (ii) non-nucleoside reverse transcriptase **inhibitors** (NNRTIs): i.e., nevirapine, delavirdine, efavirenz, emivirine (MKC-442); and (iii) protease **inhibitors** (PIs): i.e., saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, and lopinavir. In addition to the reverse transcriptase and protease step, various other events in the **HIV** replicative cycle are potential targets for chemotherapeutic intervention: (i) viral adsorption, through binding to the viral **envelope** glycoprotein **gp120** (polysulfates, polysulfonates, polyoxometalates, zintevir, negatively charged albumins, cosalane analogues); (ii) viral entry, through blockade of the viral coreceptors CXCR4 and **CCR5** [bicyclams (i.e. AMD3100), polyphemusins (T22), TAK-779, MIP-1 alpha LD78 beta

isoform], (iii) virus cell fusion, through binding to the viral glycoprotein gp41 [T-20 (DP-178), T-1249 (DP-107), siamycins, betulinic acid derivatives]; (iv) viral assembly and disassembly, through NCp7 zinc finger-targeted agents [2,2'-dithiobisbenzamides (DIBAs), azadicarbonamide (ADA) and NCp7 **peptide** mimics]; (v) proviral DNA integration, through integrase **inhibitors** such as L-chicoric acid and diketo acids (i.e. L-731,988); (vi) viral mRNA transcription, through **inhibitors** of the transcription (transactivation) process (fluoroquinolone K-12, Streptomyces product EM2487, temacrazine, CGP64222). Also, in recent years new NRTIs, NNRTIs and PIs have been developed that possess respectively improved metabolic characteristics (i.e. phosphoramidate and cyclosaligenyl pronucleotides of d4T), or increased activity against NNRTI-resistant **HIV** strains [second generation NNRTIs, such as capravirine and the novel quinoxaline, quinazolinone, phenylethylthiazolylthiourea (PETT) and emivirine (MKC-442) analogues], or, as in the case of PIs, a different, non-peptidic scaffold [i.e. cyclic urea (DMP 450), 4-hydroxy-2-pyrone (tipranavir)]. Given the multitude of molecular targets with which anti-**HIV** agents can interact, one should be cautious in extrapolating from cell-free enzymatic assays to the mode of action of these agents in intact cells. A number of compounds (i.e. zintevir and L-chicoric acid, on the one hand; and CGP64222 on the other hand) have recently been found to interact with virus-cell binding and viral entry in contrast to their proposed modes of action targeted at the integrase and transactivation process, respectively.

L16 ANSWER 43 OF 104 MEDLINE on STN

2001663073. PubMed ID: 11707878. Katy, bar the door! **HIV** entry **inhibitors**. Martinez L J. Research initiative, treatment action : RITA, (2000 Jun) 6 (2) 6-12. Journal code: 100891089. ISSN: 1520-8745. Pub. country: United States. Language: English.

L16 ANSWER 44 OF 104 MEDLINE on STN

2001653988. PubMed ID: 11696454. **Gp120**-induced Bob/GPR15 activation: a possible cause of **human immunodeficiency virus** enteropathy. Clayton F; Kotler D P; Kuwada S K; Morgan T; Stepan C; Kuang J; Le J; Fantini J. (Department of Pathology, Salt Lake Veteran's Administration, Salt Lake City, Utah 84148, USA.. drfclayton@aol.com) . American journal of pathology, (2001 Nov) 159 (5) 1933-9. Journal code: 0370502. ISSN: 0002-9440. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** (**HIV**)-infected patients often develop malabsorption and increased intestinal permeability with diarrhea, called **HIV** enteropathy, even without enteric opportunistic infections. **HIV gp120**-induced calcium signaling, microtubule loss, and physiological changes resembling **HIV** enteropathy were previously found in the HT-29 intestinal cell line. How **gp120** caused these changes was unclear. We show that the **HIV** co-receptor Bob/GPR15, unlike **CCR5** and CXCR4, is abundant at the basal surface of small intestinal epithelium. The **gp120**-induced effects on HT-29 cells were **inhibited** by anti-Bob neutralizing antibodies, the selective G protein **inhibitor** pertussis toxin, and the phospholipase **inhibitor** U73122, but not neutralizing antibodies to CXCR4. **Gp120** strains that induced signaling in HT-29 cells also induced calcium fluxes in Bob-transfected Ghost (3) cells, whereas **gp120** strains not activating HT-29 cells also did not activate Bob-transfected cells. Bob is the first **HIV** co-receptor shown to be abundantly expressed on the basolateral surface of intestinal epithelium. Although Bob is an inefficient infection-inducing co-receptor, it mediates viral strain-specific **gp120**-induced calcium signaling at low, physiologically reasonable **gp120** concentrations, up to 10,000-fold lower **gp120** concentrations than the principal co-receptors. **Gp120**-induced Bob activation is a plausible cause of **HIV** enteropathy.

L16 ANSWER 45 OF 104 MEDLINE on STN

2001647970. PubMed ID: 11700073. Molecular anatomy of **CCR5** engagement by physiologic and viral chemokines and **HIV**-1 **envelope** glycoproteins: differences in primary structural requirements for RANTES, MIP-1 alpha, and vMIP-II Binding. Navenot J M; Wang Z X; Trent J O; Murray J L; Hu Q X;

DeBeeuw D, Moore P S, Chang Y, Peiper S C. (Brown Cancer Center, University of Louisville, Louisville, KY, USA.) Journal of molecular biology, (2001 Nov 9) 313 (5) 1181-93. Journal code: 2985088R. ISSN: 0022-2836. Pub. country: England: United Kingdom. Language: English.

AB Molecular analysis of **CCR5**, the cardinal coreceptor for **HIV**-1 infection, has implicated the N-terminal extracellular domain (N-ter) and regions vicinal to the second extracellular loop (ECL2) in this activity. It was shown that residues in the N-ter are necessary for binding of the physiologic ligands, RANTES (CCL5) and MIP-1 alpha (CCL3). vMIP-II, encoded by the Kaposi's sarcoma-associated herpesvirus, is a high affinity **CCR5** antagonist, but lacks efficacy as a coreceptor **inhibitor**. Therefore, we compared the mechanism for engagement by vMIP-II of **CCR5** to its interaction with physiologic ligands. RANTES, MIP-1 alpha, and vMIP-II bound **CCR5** at high affinity, but demonstrated partial cross-competition. Characterization of 15 **CCR5** alanine scanning mutants of charged extracellular amino acids revealed that alteration of acidic residues in the distal N-ter abrogated binding of RANTES, MIP-1 alpha, and vMIP-II. Whereas mutation of residues in ECL2 of **CCR5** dramatically reduced the binding of RANTES and MIP-1 alpha and their ability to induce signaling, interaction with vMIP-II was not altered by any mutation in the exoloops of the receptor. Paradoxically, monoclonal antibodies to N-ter **epitopes** did not block chemokine binding, but those mapped to ECL2 were effective **inhibitors**. A **CCR5** chimera with the distal N-ter residues of CXCR2 bound MIP-1 alpha and vMIP-II with an affinity similar to that of the wild-type receptor. Engagement of **CCR5** by vMIP-II, but not RANTES or MIP-1 alpha blocked the binding of monoclonal antibodies to the receptor, providing additional evidence for a distinct mechanism for viral chemokine binding. Analysis of the coreceptor activity of randomly generated mouse-human **CCR5** chimeras implicated residues in ECL2 between H173 and V197 in this function. RANTES, but not vMIP-II blocked **CCR5** M-tropic coreceptor activity in the fusion assay. The insensitivity of vMIP-II binding to mutations in ECL2 provides a potential rationale to its inefficiency as an antagonist of **CCR5** coreceptor activity. These findings suggest that the molecular anatomy of **CCR5** binding plays a critical role in antagonism of coreceptor activity.

L16 ANSWER 46 OF 104 MEDLINE on STN

2001490769. PubMed ID: 11533159. Antigenically distinct conformations of CXCR4. Baribaud F; Edwards T G; Sharron M; Brelot A; Heveker N; Price K; Mortari F; Alizon M; Tsang M; Doms R W. (Department of Microbiology, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.) Journal of virology, (2001 Oct) 75 (19) 8957-67. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The major **human immunodeficiency virus** type 1 (**HIV**-1) coreceptors are the **chemokine receptors CCR5** and CXCR4. The patterns of expression of the major coreceptors and their use by **HIV**-1 strains largely explain viral tropism at the level of entry. However, while virus infection is dependent upon the presence of CD4 and an appropriate coreceptor, it can be influenced by a number of factors, including receptor concentration, affinity between **envelope gp120** and receptors, and potentially receptor conformation. Indeed, seven-transmembrane domain receptors, such as **CCR5**, can exhibit conformational heterogeneity, although the significance for virus infection is uncertain. Using a panel of monoclonal antibodies (MAbs) to CXCR4, we found that CXCR4 on both primary and transformed T cells as well as on primary B cells exhibited considerable conformational heterogeneity. The conformational heterogeneity of CXCR4 explains the cell-type-dependent ability of CXCR4 antibodies to block chemotaxis to stromal cell-derived factor 1 alpha and to **inhibit HIV**-1 infection. In addition, the MAb most commonly used to study CXCR4 expression, 12G5, recognizes only a subpopulation of CXCR4 molecules on all primary cell types analyzed. As a result, CXCR4 concentrations on these important cell types have been underestimated to date. Finally, while the factors responsible for altering CXCR4 conformation are not known, we found that they do not involve CXCR4 glycosylation, sulfation of the N-terminal domain of CXCR4, or pertussis

toxin sensitive G protein coupling. The fact that this important **HIV** 1 coreceptor exists in multiple conformations could have implications for viral entry and for the development of receptor antagonists.

L16 ANSWER 47 OF 104 MEDLINE on STN

2001487823. PubMed ID: 11530189. **Peptide** T **inhibits HIV**-1 infection mediated by the **chemokine receptor**-5 (**CCR5**). Ruff M R; Melendez-Guerrero L M; Yang Q E; Ho W Z; Mikovits J W; Pert C B; Ruscetti F A. (Department of Physiology and Biophysics, Basic Science Building, Room 215, Georgetown University School of Medicine, 3900 Reservoir Road, NW, Washington, DC 20007, USA.. ruffm@georgetown.edu) . Antiviral research, (2001 Oct) 52 (1) 63-75. Journal code: 8109699. ISSN: 0166-3542. Pub. country: Netherlands. Language: English.

AB **Peptide** T, which is derived from the V2 region of **HIV**-1, **inhibits** replication of R5 and dual-tropic (R5/X4) **HIV**-1 strains in monocyte-derived macrophages (MDMs), microglia, and primary CD4(+)T cells. Little to no **inhibition** by **peptide** T was observed with lab adapted X4 viruses such as IIIB, MN, or NL4-3 propagated in CD4(+) T cells or in the MAGI entry assay. The more clinically relevant R5/X4 early passage patient isolates were **inhibited** via either the X4 or R5 **chemokine receptors**, although **inhibition** was greater with R5 compared to X4 receptors. Virus **inhibition** ranged from 60 to 99%, depending on the assay, receptor target, viral isolate and amount of added virus. Peak **inhibitory** effects were detected at concentrations from 10(-12) to 10(-9) M. **Peptide** T acted to block viral entry as it **inhibited** in the MAGI cell assay and blocked infection in the luciferase reporter assay using **HIV** virions pseudotyped with ADA **envelope**. These results using early passage virus grown in primary cells, together with two different entry reporter assays, show that **peptide** T selectively **inhibits HIV** replication using **chemokine receptor CCR5** compared to CXC4, explaining past inconsistencies of in vitro **antiviral** effects.

L16 ANSWER 48 OF 104 MEDLINE on STN

2001462471. PubMed ID: 11507206. Sensitivity of **human immunodeficiency virus** type 1 to fusion **inhibitors** targeted to the gp41 first heptad repeat involves distinct regions of gp41 and is consistently modulated by **gp120** interactions with the coreceptor. Derdeyn C A; Decker J M; Sfakianos J N; Zhang Z; O'Brien W A; Ratner L; Shaw G M; Hunter E. (Department of Microbiology, Birmingham, Alabama 35294, USA.) Journal of virology, (2001 Sep) 75 (18) 8605-14. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB T-20 is a synthetic **peptide** that corresponds to 36 amino acids within the C-terminal heptad repeat region (HR2) of **human immunodeficiency virus** type 1 (**HIV**-1) gp41. T-20 has been shown to potently **inhibit** viral replication of **HIV**-1 both in vitro and in vivo and is currently being evaluated in a Phase III clinical trial. T-649 is an **inhibitory peptide** that also corresponds to 36 amino acids within HR2. This sequence overlaps the T-20 sequence but is shifted 10 residues toward the N terminus of gp41. Both **inhibitors** are thought to exert their **antiviral** activity by interfering with the conformational changes that occur within gp41 to promote membrane fusion following **gp120** interactions with CD4 and coreceptor molecules. We have shown previously that coreceptor specificity defined by the V3 loop of **gp120** modulates sensitivity to T-20 and that a critical region within the N-terminal heptad repeat (HR1) of gp41 is the major determinant of sensitivity (C. A. Derdeyn et al., J. Virol. 74:8358-8367, 2000). This report shows that (i) regions within gp41 distinct from those associated with T-20 sensitivity govern the baseline sensitivity to T-649 and (ii) T-649 sensitivity of chimeric viruses that contain sequences derived from CXCR4- and **CCR5**-specific **envelopes** is also modulated by coreceptor specificity. Moreover, the pattern of sensitivity of **CCR5**-specific chimeras with only minor differences in their V3 loop was consistent for both **inhibitors**, suggesting that the individual affinity for coreceptor may influence accessibility of these **inhibitors** to their target sequence. Finally, an analysis of the sensitivity of 55 primary, **inhibitor**-naive **HIV**-1 isolates found that higher concentrations of

1 20 (P < 0.001) and 1 049 (P = 0.010) were required to **inhibit** **CCR5**-specific viruses compared to viruses that utilize CXCR4. The results presented here implicate **gp120**-coreceptor interactions in driving the complex conformational changes that occur in gp41 to promote fusion and entry and suggest that sensitivity to different HR1-directed fusion **inhibitors** is governed by distinct regions of gp41 but is consistently modulated by coreceptor specificity.

L16 ANSWER 49 OF 104 MEDLINE on STN
2001434405. PubMed ID: 11244037. **gp120**: Biologic aspects of structural features. Poignard P; Saphire E O; Parren P W; Burton D R. (Department of Immunology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA.. poignard@scripps.edu) . Annual review of immunology, (2001) 19 253-74. Journal code: 8309206. ISSN: 0732-0582. Pub. country: United States. Language: English.
AB **HIV**-1 particles are decorated with a network of densely arranged **envelope** spikes on their surface. Each spike is formed of a trimer of heterodimers of the **gp120** surface and the gp41 transmembrane glycoproteins. These molecules mediate **HIV**-1 entry into target cells, initiating the **HIV**-1 replication cycle. They are a target for entry-blocking drugs and for neutralizing Abs that could contribute to vaccine protection. The crystal structure of the core of **gp120** has been recently solved. It reveals the structure of the conserved **HIV**-1 receptor binding sites and some of the mechanisms evolved by **HIV**-1 to escape Ab responses. The **gp120** consists of three faces. One is largely inaccessible on the native trimer, and two faces are exposed but apparently have low immunogenicity, particularly on primary viruses. We have modeled **HIV**-1 neutralization by a CD4 binding site monoclonal Ab, and we propose that neutralization takes place by **inhibition** of the interaction between **gp120** and the target cell membrane receptors as a result of steric hindrance. Knowledge of **gp120** structure and function should assist in the design of new drugs as well as of an effective vaccine. In the latter case, circumventing the low immunogenicity of the **HIV**-1 **envelope** spike is a major challenge.

L16 ANSWER 50 OF 104 MEDLINE on STN
2001371341. PubMed ID: 11349047. Human peripheral blood T cells, monocytes, and macrophages secrete macrophage inflammatory proteins 1alpha and 1beta following stimulation with heat-inactivated Brucella abortus. Zaitseva M; King L R; Manischewitz J; Dougan M; Stevan L; Golding H; Golding B. (Division of Viral Products, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland 20892, USA.) Infection and immunity, (2001 Jun) 69 (6) 3817-26. Journal code: 0246127. ISSN: 0019-9567. Pub. country: United States. Language: English.
AB Heat-killed Brucella abortus (HBa) has been proposed as a carrier for therapeutic vaccines for individuals with immunodeficiency, due to its abilities to induce interleukin-2 (IL-2) and gamma interferon (IFN-gamma) in both CD4(+) and CD8(+) T cells and to upregulate antigen-presenting cell functions (including IL-12 production). In the current study, we investigated the ability of HBa or lipopolysaccharide isolated from HBa (LPS-Ba) to elicit beta-chemokines, known to bind to the **human immunodeficiency virus** type 1 (**HIV**-1) coreceptor **CCR5** and to block viral cell entry. It was found that human peripheral blood mononuclear cells secreted beta-chemokines following stimulation with HBa, and this effect could not be blocked by anti-IFN-gamma neutralizing antibodies. Among purified T cells, macrophage inflammatory protein 1alpha and 1beta (MIP-1alpha and MIP-1beta, respectively) secretion was observed primarily in human CD8(+) T cells. The kinetics of beta-chemokine induction in T cells were slow (3 to 4 days). The majority of beta-chemokine-producing CD8(+) T cells also produced IFN-gamma following HBa stimulation, as determined by triple-color intracellular staining. A significant number of CD8(+) T cells contained stored MIP-1beta that was released after HBa stimulation. Both HBa and LPS-Ba stimulated high levels of MIP-1alpha and MIP-1beta production in elutriated monocytes and even higher levels in macrophages. In these cells, beta-chemokine mRNA was upregulated within 30 min and proteins were secreted within 4 h of stimulation. The

monocyte and macrophage derived beta chemokines were sufficient to block **CCR5**-dependent **HIV**-1 **envelope**-mediated cell fusion. These data suggest that, in addition to the ability of HBa to elicit antigen-specific humoral and cellular immune responses, HBa-conjugated **HIV**-1 proteins or **peptides** would also generate innate chemokines with **antiviral** activity that could limit local viral spread during vaccination in vivo.

L16 ANSWER 51 OF 104 MEDLINE on STN

2001371038. PubMed ID: 11336643. Human alpha1-acid glycoprotein binds to **CCR5** expressed on the plasma membrane of human primary macrophages. Atemezem A; Mbemba E; Vassy R; Slimani H; Saffar L; Gattegno L. (Laboratoire de Biologie Cellulaire, JE 2138, Faculte de Medecine Leonard de Vinci, Universite Paris XIII, Bobigny 93017, France.) Biochemical journal, (2001 May 15) 356 (Pt 1) 121-8. Journal code: 2984726R. ISSN: 0264-6021. Pub. country: England: United Kingdom. Language: English.

AB We have reported previously that human alpha(1)-acid glycoprotein (AGP) **inhibits** the infection of human monocyte-derived macrophages (MDM) by R5 **HIV**-1, and that a disulphide-bridged **peptide** mimicking the clade B **HIV**-1 **gp120** consensus V3 domain (V3Cs) binds specifically to **CCR5** (the major co-receptor of R5 **HIV** strains) on these cells [Seddiki, Rabehi, Benjouad, Saffar, Ferriere, Gluckman and Gattegno (1997) Glycobiology 7, 1229-1236]. The present study demonstrates that AGP binds specifically to MDM at high- and low-affinity binding sites with K(d) values of 16 nM and 4.9 microM respectively. The fact that heat denaturation of AGP only partly **inhibited** this binding (43%) suggests that protein-protein interactions are involved, as well as AGP glycans which are resistant to heat denaturation. Mannan, but not dextran, is a significant **inhibitor** (52%) of this binding, and sequential exoglycosidase treatment of AGP, which exposes penultimate mannose residues, has a strong stimulatory effect (approximately 2.8-fold). Therefore AGP glycans (probably mannose residues) are involved, at least partly, in the binding of AGP to MDM. In addition, AGP **inhibits** the binding of V3Cs and macrophage inflammatory protein-1beta (MIP-1beta) to MDM. The anti-**CCR5** monoclonal antibody 2D7, specific for the second extracellular loop of **CCR5**, also **inhibited** AGP binding (67%), whereas anti-**CCR5** antibodies specific for the C-terminus of **CCR5** region had no effect. Native AGP, like V3Cs (but not heat-denatured AGP), binds to 46 and 33-36 kDa electroblotted AGP-bound MDM membrane ligands, characterized as **CCR5** by their interactions with anti-**CCR5** antibodies and with MIP-1beta. Therefore both AGP glycans and MDM **CCR5** are involved in the binding of AGP to MDM. This suggests that the **inhibitory** effect of AGP on the infection of human primary macrophages by R5 **HIV**-1 may be related to specific binding of AGP to a macrophage membrane lectin or lectin-like component and to **CCR5**.

L16 ANSWER 52 OF 104 MEDLINE on STN

2001291050. PubMed ID: 11375057. Biological and genetic characterization of a **human immunodeficiency virus** strain resistant to CXCR4 antagonist T134. Kanbara K; Sato S; Tanuma J; Tamamura H; Gotoh K; Yoshimori M; Kanamoto T; Kitano M; Fujii N; Nakashima H. (Department of Microbiology and Immunology, Kagoshima University Dental School, 8-35-1 Sakuragaoka, Kagoshima 890-8544, Japan.) AIDS research and human retroviruses, (2001 May 1) 17 (7) 615-22. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB The **chemokine receptors** CXCR4 and **CCR5** are considered to be potential targets for the **inhibition** of **HIV**-1 replication. We have reported that T134 and T140 **inhibited** X4 **HIV**-1 infection specifically because they acted as CXCR4 antagonists. In the present study, we have generated a T134-resistant virus (trHIV-1(NL4-3)) in a cell culture with gradually increasing concentrations of the compound. The EC(50) of T134 against trHIV-1(NL4-3) recovered after 145 passages was 15 times greater than that against wild-type **HIV**-1(NL4-3). This adapted virus was resistant to other CXCR4 antagonists, T140, AMD3100, and ALX40-4C, and SDF-1; from 10 to 145 times greater than that against wild-type **HIV**-1(NL4-3). On the other hand, T134, T140, and ALX40-4C were still active against AMD3100-resistant viruses (arHIV-1(018A)). The

trHIV-1(NL4-3) contained the following mutations in the V3 loop of **gp120**: N269K, Q278T, R279K, A284V, F285L, V286Y, I288T, K290E, N293D, M294I, and Q296K; an insertion of T at 290; and Delta274-275 (SI). In addition, many other mutations were recognized in the V1, V2, and V4 domains. Thus, resistance to T134 may be the consequence of amino acid substitutions in the **envelope** glycoprotein of X4 **HIV**-1. The trHIV-1(NL4-3) could not utilize **CCR5** as an **HIV** infection coreceptor, although many amino acid substitutions were recognized. The trHIV-1(NL4-3) acquired resistance to vMIP II, which could **inhibit** both X4 and R5 **HIV**-1 infection. However, neither the ligands of **CCR5**, RANTES, and MIP-1alpha, nor a **CCR5** low molecular antagonist, TAK-779, were able to influence the infection of trHIV-1(NL4-3). Those results indicated that alternation of coreceptor usage of trHIV-1(NL4-3) was not induced.

L16 ANSWER 53 OF 104 MEDLINE on STN

2001273171. PubMed ID: 11342415. The synthetic **peptide** WKYMVm attenuates the function of the **chemokine receptors CCR5** and CXCR4 through activation of formyl **peptide** receptor-like 1. Li B Q; Wetzel M A; Mikovits J A; Henderson E E; Rogers T J; Gong W; Le Y; Ruscetti F W; Wang J M. (Intramural Research Support Program and the Laboratory of Antiviral Drug Mechanism, NCI-Screening Technologies Branch, SAIC Frederick, MD, USA.) Blood, (2001 May 15) 97 (10) 2941-7. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB The G protein-coupled 7 transmembrane (STM) chemoattractant receptors can be inactivated by heterologous desensitization. Earlier work showed that formly **peptide** receptor-like 1 (FPRL1), an STM receptor with low affinity for the bacterial chemotactic **peptide** formyl-methionyl-leucyl-phenylalamine (fMLF), is activated by **peptide** domains derived from the **human immunodeficiency virus** (**HIV**)-1 **envelope** glycoprotein **gp120** and its activation results in desensitization and down-regulation of the **chemokine receptors CCR5** and CXCR4 from monocyte surfaces. This study investigated the possibility of interfering with the function of **CCR5** or CXCR4 as **HIV**-1 coreceptors by activating FPRL1. Cell lines were established expressing FPRL1 in combination with CD4/CXCR4 or CD4/**CCR5** and the effect of a synthetic **peptide**, WKYMVm, a potent activator of formyl **peptide** receptors with preference for FPRL1 was determined. Both CXCR4 and **CCR5** were desensitized by activation of the cells with WKYMVm via a staurosporine-sensitive pathway. This desensitization of CXCR4 and **CCR5** also attenuated their capacity as the fusion cofactors for **HIV**-1 **envelope** glycoprotein and resulted in a significant **inhibition** of p24 production by cell lines infected with **HIV**-1 that use **CCR5** or CXCR4 as coreceptors. Furthermore, WKYMVm **inhibited** the infection of human peripheral monocyte-derived macrophages and CD4(+) T lymphocytes by R5 or X4 strains of **HIV**-1, respectively. These results indicate that heterologous desensitization of **CCR5** and CXCR4 by an FPRL1 agonist attenuates their major biologic functions and suggest an approach to the development of additional anti-**HIV**-1 agents. (Blood. 2001;97:2941-2947)

L16 ANSWER 54 OF 104 MEDLINE on STN

2001264730. PubMed ID: 11356961. Mapping the determinants of the **CCR5** amino-terminal sulfopeptide interaction with soluble **human immunodeficiency virus** type 1 **gp120**-CD4 complexes. Cormier E G; Tran D N; Yukhayeva L; Olson W C; Dragic T. (Microbiology and Immunology Department, Albert Einstein College of Medicine, Bronx, New York 10461, USA.) Journal of virology, (2001 Jun) 75 (12) 5541-9. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB CD4 and **CCR5** mediate fusion and entry of R5 **human immunodeficiency virus** type 1 (**HIV**-1) strains. Sulfotyrosine and other negatively charged residues in the **CCR5** amino-terminal domain (Nt) are crucial for **gp120** binding and viral entry. We previously showed that a soluble **gp120**-CD4 complex specifically binds to a **peptide** corresponding to **CCR5** Nt residues 2 to 18, with sulfotyrosines in positions 10 and 14. This sulfopeptide also **inhibits** soluble **gp120**-CD4 binding to cell surface **CCR5** as well as infection by an R5 virus. Here we show that

residues 10 to 18 constitute the minimal domain of the **CCR5** Nt that is able to specifically interact with soluble **gp120**-CD4 complexes. In addition to sulfotyrosines in positions 10 and 14, negatively charged residues in positions 11 and 18 participate in this interaction. Furthermore, the **CCR5** Nt binds to a CD4-induced surface on **gp120** that is composed of conserved residues in the V3 loop stem and the C4 domain. Binding of **gp120** to cell surface **CCR5** is further influenced by residues in the crown of the V3 loop, C1, C2, and C3. Our data suggest that **gp120** docking to **CCR5** is a multistep process involving several independent regions of the **envelope** glycoprotein and the coreceptor.

L16 ANSWER 55 OF 104 MEDLINE on STN
2001200933. PubMed ID: 11118068. Interaction between **HIV** type 1 glycoprotein 120 and CXCR4 coreceptor involves a highly conserved arginine residue in hypervariable region 3. Wang W K; Lee C N; Dudek T; Chang S Y; Zhao Y J; Essex M; Lee T H. (Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts 02115, USA.) AIDS research and human retroviruses, (2000 Nov 20) 16 (17) 1821-9. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Several seven-transmembrane **chemokine receptors** are known to function as entry coreceptors for **human immunodeficiency virus** type 1. **CCR5** and CXCR4 are the major coreceptors for non-syncytium-inducing (NSI) and syncytium-inducing (SI) viruses, respectively. During the natural course of infection, the emergence of variants with a phenotypic transition from NSI to SI and rapid disease progression is associated with expanded coreceptor usage to CXCR4. Characteristic amino acids at several positions in the hypervariable region 3 (V3) of **gp120** have been linked to CXCR4 utilization. Previously, we reported that a highly conserved arginine residue of V3 played an important role in **CCR5** utilization. In this study, the possible involvement of the same arginine residue in CXCR4 utilization was investigated. Amino acid substitutions introduced to this arginine on R5X4 viruses were found to have a significant effect on their utilization of CXCR4. These results, taken together with those reported previously, suggest that this highly conserved arginine may contribute to the functional convergence of chemokine coreceptor utilization by human immunodeficiency viruses and may represent a unique target for future **antiviral** design.

L16 ANSWER 56 OF 104 MEDLINE on STN
2001195092. PubMed ID: 11178961. V3 induces in human normal cell populations an accelerated macrophage-mediated proliferation--apoptosis phenomenon of effector T cells when they respond to their cognate antigen. Zafiropoulos A; Baritaki S; Sioumpara M; Spandidos D A; Krambovitis E. (Department of Applied Biochemistry and Immunology, Institute of Molecular Biology and Biotechnology, Vassilika Vouton, Heraklion, Crete, Greece.) Biochemical and biophysical research communications, (2001 Feb 16) 281 (1) 63-70. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB The semi-conserved domain of V3 of **HIV**-1 was synthesised in a lipopeptide form to be presented on the surface of liposome particles. Composite liposomes were constructed with entrapped tetanus toxoid as a recall antigen (lipo-V3/TT liposomes) to study the influence of V3 on effector T cells of human normal peripheral lymphocyte populations. We demonstrated that lipo-V3/TT liposomes induce a V3-specific response characterised by an early, enhanced proliferation of effector CD4+ T cells, followed by a sharp apoptosis. The phenomenon required the presence of monocyte-derived macrophages and CD4+ T cells, but it was qualitatively and quantitatively distinct from the normal soluble antigen-mediated antigen presenting cell: T cell interaction. Presence of the beta-chemokine RANTES in the culture medium **inhibited** the phenomenon, suggesting that V3 plays a costimulatory role that involves the **chemokine receptor CCR5** pathway during the process of antigen presentation to T cells. This observation may be very important if it occurs also in **HIV**-1 infection, as it may explain the selective and progressive depletion of non-infected effector CD4+ T cells.

L16 ANSWER 57 OF 104 MEDLINE on STN
2001191023. PubMed ID: 11152302. Ion channel activation by SPC3, a **peptide** derived from the **HIV**-1 **gp120** V3 loop. Carlier E; Mabrouk K; Moulard M; Fajloun Z; Rochat H; De Waard M; Sabatier J M. (INSERM U464, Laboratoire de Neurobiologie des Canaux Ioniques, Faculte de Medicine Nord, Marseille, France.) journal of peptide research : official journal of the American Peptide Society, (2000 Dec) 56 (6) 427-37. Journal code: 9707067. ISSN: 1397-002X. Pub. country: Denmark. Language: English.

AB SPC3 is a multibranched **peptide** containing eight identical GPGRAF motifs which are derived from the **human immunodeficiency virus** (**HIV**)-1 **gp120** V3 loop consensus sequence. This molecule was reported to prevent the infection of CD4+ cells by various **HIV**-1 and **HIV**-2 strains. However, the molecular mode of action of SPC3 remains unclear. Here, we investigated the possibility that SPC3 could interact with alpha/beta-**chemokine receptors** following observations that, first, the V3 loop is likely to be involved in alpha/beta-**chemokine receptor**-dependent **HIV** entry and, second, natural ligands of these receptors are potent **inhibitors** of cell infection. To address this point, we examined the effects of SPC3 on Xenopus oocytes either uninjected or expressing exogenous human CXCR4 alpha-**chemokine receptors**. Extracellular applications of micromolar concentrations of SPC3 onto Xenopus oocytes trigger potent inward chloride currents which can be **inhibited** by increasing extracellular Ca2+ concentration. This effect can be blocked by chloride channel antagonists and is highly specific to SPC3 as it is not triggered by structural analogs of SPC3. The SPC3-induced chloride conductance in oocytes is alpha/beta-**chemokine receptor** dependent because: (i) SPC3 alters the sensitivity of this channel to external applications of human recombinant MIP-1alpha, a natural ligand of human **CCR5** receptor, and (ii) the amplitude of the inward current could be increased by the expression of exogenous human CXCR4 **chemokine receptor**. The effect of SPC3 appears to rely on the activation of a phospholipase A2 signaling pathway, but is not affected by changes in cytosolic Ca2+ concentration, or by alterations in Gi/Go protein, adenylate cyclase, phospholipase C or protein kinase C activity. Altogether, the data indicate that SPC3 is capable of activating a surface alpha/beta-chemokine-like receptor-mediated signaling pathway in competent cells, thereby triggering, either directly or indirectly, a Ca2+-inactivated chloride conductance.

L16 ANSWER 58 OF 104 MEDLINE on STN
2001112825. PubMed ID: 11150506. The possible involvement of CXCR4 in the **inhibition** of **HIV**-1 infection mediated by DP178/gp41. Xu Y; Zhang X; Matsuoka M; Hattori T. (Laboratory of Virus Immunology, Institute for Virus Research, Kyoto University, Kyoto, Japan.) FEBS letters, (2000 Dec 29) 487 (2) 185-8. Journal code: 0155157. ISSN: 0014-5793. Pub. country: Netherlands. Language: English.

AB The N- (N36/DP107) and C-terminal **peptides** (C34/DP178) from two alpha-helical domains of **human immunodeficiency virus** type 1 (**HIV**-1) gp41 **inhibited HIV** infection. A single-round infection using pseudotyped virus clarified that a greater amount of gp41-derived **peptides** was necessary for the **inhibition** of R5 virus (ADA) infection than for that of X4 virus (LAI) infection. Furthermore, R5X4 virus (89.6) infection via **CCR5** needs more **peptides** for **inhibition** than its infection via CXCR4 does. A high sensitivity of X4 virus was partially ascribed to the **inhibition** of the 12G5 binding to CXCR4 by DP178LAI.

L16 ANSWER 59 OF 104 MEDLINE on STN
2001092646. PubMed ID: 11134270. Potent, broad-spectrum **inhibition** of **human immunodeficiency virus** type 1 by the **CCR5** monoclonal antibody PRO 140. Trkola A; Ketas T J; Nagashima K A; Zhao L; Cilliers T; Morris L; Moore J P; Maddon P J; Olson W C. (The Aaron Diamond AIDS Research Center, New York, USA.) Journal of virology, (2001 Jan) 75 (2) 579-88. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **CCR5** serves as a requisite fusion coreceptor for clinically relevant

strains of **human immunodeficiency virus** type 1 (**HIV** 1) and provides a promising target for **antiviral** therapy. However, no study to date has examined whether monoclonal antibodies, small molecules, or other nonchemokine agents possess broad-spectrum activity against the major genetic subtypes of **HIV**-1. PRO 140 (PA14) is an anti-**CCR5** monoclonal antibody that potently **inhibits HIV**-1 entry at concentrations that do not affect **CCR5**'s **chemokine receptor** activity. In this study, PRO 140 was tested against a panel of primary **HIV**-1 isolates selected for their genotypic and geographic diversity. In quantitative assays of viral infectivity, PRO 140 was compared with RANTES, a natural **CCR5** ligand that can **inhibit HIV**-1 entry by receptor downregulation as well as receptor blockade. Despite their divergent mechanisms of action and binding **epitopes** on **CCR5**, low nanomolar concentrations of both PRO 140 and RANTES **inhibited** infection of primary peripheral blood mononuclear cells (PBMC) by all **CCR5**-using (R5) viruses tested. This is consistent with there being a highly restricted pattern of **CCR5** usage by R5 viruses. In addition, a panel of 25 subtype C South African R5 viruses were broadly **inhibited** by PRO 140, RANTES, and TAK-779, although approximately 30-fold-higher concentrations of the last compound were required. Interestingly, significant **inhibition** of a dualtropic subtype C virus was also observed. Whereas PRO 140 potently **inhibited HIV**-1 replication in both PBMC and primary macrophages, RANTES exhibited limited **antiviral** activity in macrophage cultures. Thus **CCR5**-targeting agents such as PRO 140 can demonstrate potent and genetic-subtype-independent anti-**HIV**-1 activity.

L16 ANSWER 60 OF 104 MEDLINE on STN

2001059294. PubMed ID: 10945227. **HIV**-1 gp41 and type I interferon: sequence homology and biological as well as clinical implications. Chen Y H; Xiao Y; Dierich M P. (Laboratory of Immunology, Research Centre of Medical Research and School of Life Science and Engineering, Tsinghua University, Beijing, PR China.) Immunologic research, (2000) 22 (1) 61-6. Ref: 38. Journal code: 8611087. ISSN: 0257-277X. Pub. country: United States. Language: English.

AB **HIV**-1 gp41-like human type I interferon (IFN) could **inhibit** lymphocyte proliferation and up-modulate MHC class I and II and ICAM-1 molecule expression. Sequence comparison indicates that a similar **epitope** RILAV-YLKD exists between N-domain of gp41 and two regions in IFN-alpha(aa29-35 and 113-129), IFN-beta (aa31-37 and 125-138) and IFN-omega (aa29-35 and 123-136), which was shown to form IFN-alpha/beta-receptor binding site. Weak sequence similarity was also found to exist in both regions on gp41 and type I IFN of murine and bovine. Experimental studies indicated that a common immunological **epitope** exists between gp41 and IFN-alpha and -beta. Antibodies against human IFN-alpha and -beta recognized the common immunological **epitope** and **inhibited** gp41-binding to the potential cellular receptor protein p45. Moreover, the polyclonal antibody to IFN-beta completely **inhibited** gp41-binding to human T, B cells and monocytic cells, while IFN-alpha could only **inhibit** this binding incompletely. It was interestingly observed that human IFN-beta after preincubating with cells could incompletely **inhibit** the binding of gp41 to human B cells and monocytic cells, and very weakly **inhibit** the binding to human T cells, indicating that the receptor for IFN-beta-binding may be involved in gp41 binding. This potential relationship may be based on the amino acid sequence homology in the receptor binding region between gp41 and IFN-beta. It was observed that the increased levels of antibodies against human IFN-alpha and -beta exist in **HIV**-1-infected individuals and are associated with the common **epitope** on gp41. Besides, several studies provided experimental evidence that the common immunological **epitope** could induce protective activity against **HIV**-1. The IFN-alpha-based vaccine has showed a significant reduction of disease progression in IFN-alpha-vaccine-treated **HIV**-infected patients. Recent experimental evidence indicates that gp41 and IFN-beta were involved in downregulation of **CCR5** expression and induction of cell activation or signal transduction. Whether it may be performed by a similar mechanism is still to be investigated.

L16 ANSWER 61 OF 104 MEDLINE on STN

2001051383. PubMed ID: 11049991. Interferon gamma and interleukin 6 modulate the susceptibility of macrophages to **human immunodeficiency virus** type 1 infection. Zaitseva M; Lee S; Lapham C; Taffs R; King L; Romantseva T; Manischewitz J; Golding H. (Division of Viral Products, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD 20892, USA.. zaitseva@cber.fda.gov) . Blood, (2000 Nov 1) 96 (9) 3109-17. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB The effect of interferon gamma (IFN-gamma) and interleukin 6 (IL-6) on infection of macrophages with **human immunodeficiency virus** type 1 (**HIV**-1) was investigated. By using a polymerase chain reaction-based viral entry assay and viral infectivity assay, it was demonstrated that IL-6 and IFN-gamma augmented susceptibility of monocyte-derived macrophages (MDMs) to infection with T-cell tropic CXCR4-utilizing (X4) **HIV**-1 strains. Consistent with this finding, IFN-gamma and IL-6 augmented fusion of MDMs with T-tropic **envelope**-expressing cells. The enhanced fusion of cytokine-treated MDMs with T-tropic **envelopes** was **inhibited** by the CXCR4 ligand, SDF-1, and by T22 **peptide**. IFN-gamma and IL-6 did not affect expression of surface CXCR4 or SDF-1-induced Ca(++) flux in MDMs. In contrast to the effect of IFN-gamma on the infection of MDMs with X4 strains, IFN-gamma **inhibited** viral entry and productive infection of MDMs with macrophage-tropic (M-tropic) **HIV**-1. Consistent with this finding, IFN-gamma induced a decrease in fusion with M-tropic **envelopes** that correlated with a modest reduction in surface **CCR5** and CD4 on MDMs. It was further demonstrated that macrophage inflammatory protein (MIP)-1alpha and MIP-beta secreted by cytokine-treated MDMs augmented their fusion with T-tropic-expressing cells and **inhibited** their fusion with M-tropic **envelope**-expressing cells. These data indicate that proinflammatory cytokines, which are produced during opportunistic infections or sexually transmitted diseases, may predispose macrophages to infection with X4 strains that, in turn, could accelerate disease progression.

L16 ANSWER 62 OF 104 MEDLINE on STN

2001038229. PubMed ID: 10938094. A tyrosine-sulfated **peptide** based on the N terminus of **CCR5** interacts with a CD4-enhanced **epitope** of the **HIV**-1 **gp120 envelope** glycoprotein and **inhibits HIV**-1 entry. Farzan M; Vasilieva N; Schnitzler C E; Chung S; Robinson J; Gerard N P; Gerard C; Choe H; Sodroski J. (Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, and Department of Pathology, Harvard Medical School, Boston, MA 02115, USA.. farzan@mbcrr.harvard.edu) . Journal of biological chemistry, (2000 Oct 27) 275 (43) 33516-21. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The sequential association of the **human immunodeficiency virus** type 1 (**HIV**-1) **envelope** glycoprotein **gp120** with CD4 and a seven-transmembrane segment coreceptor such as **CCR5** or CXCR4 initiates entry of the virus into its target cell. The N terminus of **CCR5**, which contains several sulfated tyrosines, plays a critical role in the CD4-dependent association of **gp120** with **CCR5** and in viral entry. Here we demonstrate that a tyrosine-sulfated **peptide** based on the N terminus of **CCR5**, but not its unsulfated analogue, **inhibits** infection of macrophages and peripheral blood mononuclear cells by **CCR5**-dependent, but not CXCR4-dependent, **HIV**-1 isolates. The sulfated **peptide** also **inhibited** the association of **CCR5**-expressing cells with **gp120**-soluble CD4 complexes and, less efficiently, with MIP-1alpha. Moreover, this **peptide inhibited** the precipitation of **gp120** by 48d and 23e antibodies, which recognize CD4-inducible **gp120 epitopes**, but not by several other antibodies that recognize proximal **epitopes**. The ability of the sulfated **peptide** to block 48d association with **gp120** was dependent in part on seven tropism-determining residues in the third variable (V3) and fourth conserved (C4) domains of **gp120**. These data underscore the important role of the N-terminal sulfate moieties of **CCR5** in the entry of R5 **HIV**-1 isolates and localize a critical contact between **gp120** and **CCR5**.

L16 ANSWER 63 OF 104 MEDLINE on STN
2001019049. PubMed ID: 11023526. Down-regulation of the **chemokine receptor CCR5** by activation of chemotactic formyl **peptide** receptor in human monocytes. Shen W; Li B; Wetzel M A; Rogers T J; Henderson E E; Su S B; Gong W; Le Y; Sargeant R; Dimitrov D S; Oppenheim J J; Wang J M. (Laboratory of Molecular Immunoregulation, Division of Basic Sciences, National Cancer Institute, Frederick, MD 21702-1201, USA.) Blood, (2000 Oct 15) 96 (8) 2887-94. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Interactions between cell surface receptors are important regulatory elements in the complex host responses to infections. In this study, it is shown that a classic chemotactic factor, the bacterial chemotactic **peptide** N-formyl-methionyl-leucylphenyl-alanine (fMLF), rapidly induced a protein-kinase-C-mediated serine phosphorylation and down-regulation of the **chemokine receptor CCR5**, which serves as a major **human immunodeficiency virus** (**HIV**)-1 coreceptor. The fMLF binding to its receptor, formyl **peptide** receptor (FPR), resulted in significant attenuation of cell responses to **CCR5** ligands and in **inhibition** of **HIV**-1-**envelope**-glycoprotein-mediated fusion and infection of cells expressing CD4, **CCR5**, and FPR. The finding that the expression and function of **CCR5** can be regulated by **peptides** that use an unrelated receptor may provide a novel approach to the design of anti-inflamatory and **antiretroviral** agents. (Blood. 2000;96:2887-2894)

L16 ANSWER 64 OF 104 MEDLINE on STN
2000459388. PubMed ID: 10954535. Sensitivity of **human immunodeficiency virus** type 1 to the fusion **inhibitor** T-20 is modulated by coreceptor specificity defined by the V3 loop of **gp120**. Derdeyn C A; Decker J M; Sfakianos J N; Wu X; O'Brien W A; Ratner L; Kappes J C; Shaw G M; Hunter E. (Department of Microbiology, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA.) Journal of virology, (2000 Sep) 74 (18) 8358-67. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB T-20 is a synthetic **peptide** that potently **inhibits** replication of **human immunodeficiency virus** type 1 by interfering with the transition of the transmembrane protein, gp41, to a fusion active state following interactions of the surface glycoprotein, **gp120**, with CD4 and coreceptor molecules displayed on the target cell surface. Although T-20 is postulated to interact with an N-terminal heptad repeat within gp41 in a trans-dominant manner, we show here that sensitivity to T-20 is strongly influenced by coreceptor specificity. When 14 T-20-naive primary isolates were analyzed for sensitivity to T-20, the mean 50% **inhibitory** concentration (IC(50)) for isolates that utilize **CCR5** for entry (R5 viruses) was 0.8 log(10) higher than the mean IC(50) for CXCR4 (X4) isolates (P = 0. 0055). Using NL4.3-based **envelope** chimeras that contain combinations of **envelope** sequences derived from R5 and X4 viruses, we found that determinants of coreceptor specificity contained within the **gp120** V3 loop modulate this sensitivity to T-20. The IC(50) for all chimeric **envelope** viruses containing R5 V3 sequences was 0.6 to 0.8 log(10) higher than that for viruses containing X4 V3 sequences. In addition, we confirmed that the N-terminal heptad repeat of gp41 determines the baseline sensitivity to T-20 and that the IC(50) for viruses containing GIV at amino acid residues 36 to 38 was 1.0 log(10) lower than the IC(50) for viruses containing a G-to-D substitution. The results of this study show that **gp120**-coreceptor interactions and the gp41 N-terminal heptad repeat independently contribute to sensitivity to T-20. These results have important implications for the therapeutic uses of T-20 as well as for unraveling the complex mechanisms of virus fusion and entry.

L16 ANSWER 65 OF 104 MEDLINE on STN
2000457650. PubMed ID: 10940916. The role of gammadelta T cells in generating **antiviral** factors and beta-chemokines in protection against mucosal simian immunodeficiency virus infection. Lehner T; Mitchell E; Bergmeier L; Singh M; Spallek R; Cranage M; Hall G; Dennis M; Villinger F;

Wang T. (Department of Immunobiology, Guy's, King's and St. Thomas' Hospital Medical School, London, GB.. thomas.lehner@kcl.ac.uk) . European journal of immunology, (2000 Aug) 30 (8) 2245-56. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB In view of the role of gammadelta(+) T cells in mucosal protection against infection, the proportion of gamma delta T cells was examined in cells eluted from lymphoid and mucosal tissues of macaques immunized with simian immunodeficiency virus (SIV) **gp120** and p27 in alum and challenged with live SIV by the rectal mucosal route. This revealed a significant increase in gammadelta T cells eluted from the rectal mucosa ($p < 0.01$) and the related iliac lymph nodes ($p < 0.0001$) in protected as compared with infected macaques. Preferential homing of PKH-26-labeled gammadelta(+) T cells from the primed iliac lymph nodes to the rectal and cervico-vaginal mucosa was demonstrated after targeted iliac lymph node as compared with i. m. immunization. Investigations of the mechanism of protection revealed that gammadelta(+) T cells can generate **antiviral** factors, RANTES, macrophage inflammatory protein (MIP)-1alpha and MIP-1beta which can prevent SIV infection by binding to the **CCR5** coreceptors. Up-regulation of gammadelta(+) T cells was demonstrated by immunization of macaques with heat shock protein (HSP)70 linked to **peptides** and with granulocyte-macrophage colony-stimulating factor (GM-CSF). This was confirmed by in vitro studies showing that GM-CSF can up-regulate gammadelta(+) T cells from macaques immunized with HSP-linked **peptides** but not those from naive animals. We suggest that a novel strategy of immunization with HSP70 linked to antigen may generate both cognate immunity to the antigen and innate immunity by virtue of up-regulation of gammadelta(+) T cells. These cells generate **antiviral** factors and the three beta-chemokines that prevent binding and transmission of SIV or M-tropic **HIV** by the **CCR5** coreceptor.

L16 ANSWER 66 OF 104 MEDLINE on STN

2000456121. PubMed ID: 10835604. Paramagnetic proteoliposomes containing a pure, native, and oriented seven-transmembrane segment protein, **CCR5**. Mirzabekov T; Kontos H; Farzan M; Marasco W; Sodroski J. (Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, 44 Binney St., Boston, MA 02115, USA.) Nature biotechnology, (2000 Jun) 18 (6) 649-54. Journal code: 9604648. ISSN: 1087-0156. Pub. country: United States. Language: English.

AB Seven-transmembrane segment, G protein-coupled receptors play central roles in a wide range of biological processes, but their characterization has been hindered by the difficulty of obtaining homogeneous preparations of native protein. We have created paramagnetic proteoliposomes containing pure and oriented **CCR5**, a seven-transmembrane segment protein that serves as the principal coreceptor for **human immunodeficiency virus** (**HIV**-1). The **CCR5** proteoliposomes bind the **HIV**-1 **gp120** **envelope** glycoprotein and conformation-dependent antibodies against **CCR5**. The binding of **gp120** was enhanced by a soluble form of the other **HIV**-1 receptor, CD4, but did not require additional cellular proteins. Paramagnetic proteoliposomes are uniform in size, stable in a broad range of salt concentrations and pH, and can be used in FACS and competition assays typically applied to cells. Integral membrane proteins can be inserted in either orientation into the liposomal membrane. The magnetic properties of these proteoliposomes facilitate rapid buffer exchange useful in multiple applications. As an example, the **CCR5**-proteoliposomes were used to select **CCR5**-specific antibodies from a recombinant phage display library. Thus, paramagnetic proteoliposomes should be useful tools in the analysis of membrane protein interactions with extracellular and intracellular ligands, particularly in establishing screens for **inhibitors**.

L16 ANSWER 67 OF 104 MEDLINE on STN

2000429918. PubMed ID: 10933700. Characterization and **epitope** mapping of neutralizing monoclonal antibodies produced by immunization with oligomeric simian immunodeficiency virus **envelope** protein. Edinger A L; Ahuja M; Sung T; Baxter K C; Haggarty B; Doms R W; Hoxie J A. (Department

of Pathology and Laboratory Medicine, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.) Journal of virology, (2000 Sep) 74 (17) 7922-35. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB In an attempt to generate broadly cross-reactive, neutralizing monoclonal antibodies (MAbs) to simian immunodeficiency virus (SIV), we compared two immunization protocols using different preparations of oligomeric SIV **envelope** (**Env**) glycoproteins. In the first protocol, mice were immunized with soluble gp140 (sgp140) from CP-MAC, a laboratory-adapted variant of SIVmacBK28. Hybridomas were screened by enzyme-linked immunosorbent assay, and a panel of 65 MAbs that recognized **epitopes** throughout the **Env** protein was generated. In general, these MAbs detected **Env** by Western blotting, were at least weakly positive in fluorescence-activated cell sorting (FACS) analysis of **Env**-expressing cells, and preferentially recognized monomeric **Env** protein. A subset of these antibodies directed toward the V1/V2 loop, the V3 loop, or nonlinear **epitopes** were capable of neutralizing CP-MAC, a closely related isolate (SIVmac1A11), and/or two more divergent strains (SIVsmDeltaB670 CL3 and SIVsm543-3E). In the second protocol, mice were immunized with unfixed CP-MAC-infected cells and MAbs were screened for the ability to **inhibit** cell-cell fusion. In contrast to MAbs generated against sgp140, the seven MAbs produced using this protocol did not react with **Env** by Western blotting and were strongly positive by FACS analysis, and several reacted preferentially with oligomeric **Env**. All seven MAbs potently neutralized SIVmac1A11, and several neutralized SIVsmDeltaB670 CL3 and/or SIVsm543-3E. MAbs that **inhibited gp120** binding to CD4, **CCR5**, or both were identified in both groups. MAbs to the V3 loop and one MAb reactive with the V1/V2 loop interfered with **CCR5** binding, indicating that these regions of **Env** play similar roles for SIV and **human immunodeficiency virus**. Remarkably, several of the MAbs generated against infected cells blocked **CCR5** binding in a V3-independent manner, suggesting that they may recognize a region analogous to the conserved coreceptor binding site in **gp120**. Finally, all neutralizing MAbs blocked infection through the alternate coreceptor STRL33 much more efficiently than infection through **CCR5**, a finding that has important implications for SIV neutralization assays using **CCR5**-negative human T-cell lines.

L16 ANSWER 68 OF 104 MEDLINE on STN

2000419632. PubMed ID: 10933940. Characterization of anti-**CCR5** ribozyme-transduced CD34+ hematopoietic progenitor cells in vitro and in a SCID-hu mouse model in vivo. Bai J; Gorantla S; Banda N; Cagnon L; Rossi J; Akkina R. (Department of Pathology, Colorado State University, Fort Collins 80523, USA.) Molecular therapy : journal of the American Society of Gene Therapy, (2000 Mar) 1 (3) 244-54. Journal code: 100890581. ISSN: 1525-0016. Pub. country: United States. Language: English.

AB The cellular entry of **HIV** is mediated by the specific interaction of viral **envelope** glycoproteins with the cell-surface marker CD4 and a **chemokine receptor** (**CCR5** or CXCR4). Individuals with a 32-base-pair (bp) deletion in the **CCR5** coding region, which results in a truncated **peptide**, show resistance to **HIV**-1 infection. This suggests that the downregulation of **CCR5** expression on target cells may prevent **HIV** infection. Therefore, ribozymes that **inhibit** the **CCR5** expression offer a novel approach for anti-**HIV** gene therapy. To assess the effect of an anti-**CCR5** ribozyme (R5Rbz) on macrophage differentiation, CD34+ hematopoietic progenitor cells were transduced with a retroviral vector carrying RSRbz and allowed to differentiate in the presence of appropriate cytokines. R5Rbz-transduced CD34+ cells differentiated normally into mature macrophages that carried CD14 and CD4 surface markers, expressed the anti-**CCR5** ribozyme, and showed significant resistance to viral infection upon challenge with the **HIV**-1 BaL strain. Using an in vivo thymopoiesis model, the effect of RSRbz on stem cell differentiation into thymocytes was evaluated by reconstituting SCID-hu mice thymic grafts with ribozyme-transduced CD34+ cells. FACS analysis of cell biopsies at 4 and 6 weeks postengraftment for HLA, CD4, and CD8 markers showed comparable levels of reconstitution and similar percentages of subpopulations of thymocytes between grafts receiving R5Rbz-transduced and control CD34+

cells. RT-PCR assays demonstrated the expression of the anti-**CCR5** ribozyme in CD4+, CD8+, and CD4+/CD8+ thymocyte subsets derived from RSRbz-transduced CD34+ cells. These results indicate that anti-**CCR5** ribozyme can be introduced into hematopoietic stem cells without adverse effects on their subsequent lineage-specific differentiation and maturation. The expression of anti-**CCR5** ribozymes in **HIV**-1 target cells offers a novel gene therapy strategy to control **HIV** infection.

L16 ANSWER 69 OF 104 MEDLINE on STN
2000387867. PubMed ID: 10846110. Coreceptor-dependent **inhibition** of the cell fusion activity of simian immunodeficiency virus **Env** proteins. Yang C; Yang Q; Compans R W. (Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, Georgia 30322, USA.) Journal of virology, (2000 Jul) 74 (13) 6217-22. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.
AB The cytoplasmic tail (R **peptide**) sequence is able to regulate the fusion activity of the murine leukemia virus (MuLV) **envelope** (**Env**) protein. We have previously shown that this sequence exerts a profound **inhibitory** effect on the fusion activity of simian immunodeficiency virus (SIV)-MuLV chimeric **Env** proteins which contain the extracellular and transmembrane domains of the SIV **Env** protein. Recent studies have shown that SIV can utilize several alternative cellular coreceptors for its fusion and entry into the cell. We have investigated the fusion activity of SIV and SIV-MuLV chimeric **Env** proteins using cells that express different coreceptors. HeLa cells were transfected with plasmid constructs that carry the SIV or SIV-MuLV chimeric **Env** protein genes and were overlaid with either CEMx174 cells or Ghost Gpr15 cells, which express the Gpr15 coreceptor for SIV, or Ghost **CCR5** cells, which express **CCR5**, an alternate coreceptor for SIV. The R-**peptide** sequence in the SIV-MuLV chimeric proteins was found to **inhibit** the fusion with CEMx174 cells or Ghost Gpr15 cells. However, a significant level of fusion was still observed when HeLa cells expressing the chimeric **Env** proteins were cocultivated with Ghost **CCR5** cells. These results show that the R-**peptide** sequence exerts differential effects on the fusion activity of SIV **Env** proteins using target cells that express alternative coreceptors.

L16 ANSWER 70 OF 104 MEDLINE on STN
2000283899. PubMed ID: 10823934. Specific interaction of **CCR5** amino-terminal domain **peptides** containing sulfotyrosines with **HIV**-1 **envelope** glycoprotein **gp120**. Cormier E G; Persuh M; Thompson D A; Lin S W; Sakmar T P; Olson W C; Dragic T. (Albert Einstein College of Medicine, Microbiology and Immunology Department, 1300 Morris Park Avenue, Bronx, NY 10461, USA.) Proceedings of the National Academy of Sciences of the United States of America, (2000 May 23) 97 (11) 5762-7. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.
AB The **HIV**-1 **envelope** glycoprotein **gp120** interacts consecutively with CD4 and the **CCR5** coreceptor to mediate the entry of certain **HIV**-1 strains into target cells. Acidic residues and sulfotyrosines in the amino-terminal domain (Nt) of **CCR5** are crucial for viral fusion and entry. We tested the binding of a panel of **CCR5** Nt **peptides** to different soluble **gp120**/CD4 complexes and anti-**CCR5** mAbs. The tyrosine residues in the **peptides** were sulfated, phosphorylated, or unmodified. None of the **gp120**/CD4 complexes associated with **peptides** containing unmodified or phosphorylated tyrosines. The **gp120**/CD4 complexes containing **envelope** glycoproteins from isolates that use **CCR5** as a coreceptor associated with Nt **peptides** containing sulfotyrosines but not with **peptides** containing sulfotyrosines in scrambled Nt sequences. Finally, only **peptides** containing sulfotyrosines **inhibited** the entry of an R5 isolate. Our data show that proper posttranslational modification of the **CCR5** Nt is required for **gp120** binding and viral entry. More importantly, the Nt domain determines the specificity of the interaction between **CCR5** and gp120s from isolates that use this coreceptor.

L16 ANSWER 71 OF 104 MEDLINE on STN
2000240073. PubMed ID: 10775626. Variable sensitivity of **CCR5**-tropic

human immunodeficiency virus type 1 isolates to **inhibition** by RANTES analogs. Torre V S; Marozsan A J; Albright J L; Collins K R; Hartley O; Offord R E; Quinones-Mateu M E; Arts E J. (Division of Infectious Diseases, Department of Medicine, Case Western Reserve University, Cleveland, Ohio 44106, USA.) Journal of virology, (2000 May) 74 (10) 4868-76. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Aminooxypentane (AOP)-RANTES efficiently and specifically blocks entry of non-syncytium-inducing (NSI), **CCR5**-tropic (R5) **human immunodeficiency virus** type 1 (**HIV**-1) into host cells. **Inhibition** appears to be mediated by increased intracellular retention of the **CCR5** coreceptor- AOP-RANTES complex and/or competitive binding of AOP-RANTES with NSI R5 **HIV**-1 isolates for **CCR5**. Although AOP-RANTES and other beta-chemokine analogs are potent **inhibitors**, the extreme heterogeneity of the **HIV**-1 **envelope** glycoproteins (**gp120** and gp41) and variable coreceptor usage may affect the susceptibility of variant **HIV**-1 strains to these drugs. Using the same peripheral blood mononuclear cells (PBMC) with all isolates, we observed a significant variation in AOP-RANTES **inhibition** of 13 primary NSI R5 isolates; 50% **inhibitory** concentrations (IC(50)) ranged from 0.04 nM with **HIV**-1(A-92RW009) to 1.3 nM with **HIV**-1(B-BaL). Experiments performed on the same isolate (**HIV**-1(B-BaL)) with PBMC from different donors revealed no isolate-specific variation in AOP-RANTES IC(50) values but did show a considerable difference in virus replication efficiency. Exclusive entry via the **CCR5** coreceptor by these NSI R5 isolates suggests that variable **inhibition** by AOP-RANTES is not due to alternative coreceptor usage but rather differential **CCR5** binding. Analysis of the **envelope** V3 loop sequence linked a threonine or arginine at position 319 (numbering based on the HXB2 genome) with AOP-RANTES resistance. With the exception of one isolate, A319 was associated with increased sensitivity to AOP-RANTES **inhibition**. Distribution of AOP-RANTES IC(50) values with these isolates has promoted ongoing screens for new **CCR5** agonists that show broad **inhibition** of **HIV**-1 variants.

L16 ANSWER 72 OF 104 MEDLINE on STN

2000234582. PubMed ID: 10774549. Coreceptor usage and RANTES sensitivity of non-syncytium-inducing **HIV**-1 isolates obtained from patients with AIDS. Jansson M; Backstrom E; Bjorndal A; Holmberg V; Rossi P; Fenyo E M; Popovic M; Albert J; Wigzell H. (Microbiology and Tumorbiology Center, Karolinska Institute, Stockholm, Sweden.. marjan@mbcrr.harvard.edu) . Journal of human virology, (1999 Nov-Dec) 2 (6) 325-38. Journal code: 9805755. ISSN: 1090-9508. Pub. country: United States. Language: English.

AB OBJECTIVES: The biologic phenotype of **HIV**-1 primary isolates obtained from approximately 50% of patients who progress to AIDS switches from non-syncytium-inducing (NSI) to syncytium-inducing (SI). We evaluated possible associations between virus coreceptor usage, sensitivity to **inhibition** by beta-chemokines, and disease progression of patients who continue to yield NSI isolates after developing AIDS. STUDY DESIGN/METHODS: Sequential virus isolates were analyzed for biologic phenotype using the MT-2 cell assay, for sensitivity to beta-chemokines using RANTES **inhibition**, and for coreceptor usage using U87.CD4 and GHOST.CD4 cells expressing different chemokine/orphan receptors or donor peripheral blood mononuclear cells (PBMC) defective in **CCR5** expression. In addition, the **env** V3 region was sequenced and the length of the V2 region determined. RESULTS: All NSI isolates, regardless of patient status at time of isolation, were dependent on **CCR5** expression for cell entry. Furthermore, there was no indication of broadened coreceptor usage of NSI isolates obtained from persons with late-stage AIDS. A majority of NSI isolates remained RANTES sensitive; however, virus variants with reduced sensitivity were observed. The V2 lengths and the V3 sequences exhibited no or minor changes at analysis of sequential NSI isolates. CONCLUSIONS: Our data suggest that NSI isolates obtained from AIDS patients remain **CCR5** dependent (ie, R5) and, in many cases, also remain sensitive to RANTES **inhibition**. However, virus variants with decreased sensitivity to RANTES **inhibition** may evolve during disease progression, not only as a result of a switch from NSI to SI but also in patients who

develop AIDS while continuing to maintain R5 isolates.

L16 ANSWER 73 OF 104 MEDLINE on STN
2000225674. PubMed ID: 10760806. Monoclonal antibody screening of a phage-displayed random **peptide** library reveals mimotopes of **chemokine receptor CCR5**: implications for the tertiary structure of the receptor and for an N-terminal binding site for **HIV**-1 **gp120**. Konigs C; Rowley M J; Thompson P; Myers M A; Scealy M; Davies J M; Wu L; Dietrich U; Mackay C R; Mackay I R. (Department of Biochemistry and Molecular Biology, Monash University, Clayton, Australia.) European journal of immunology, (2000 Apr) 30 (4) 1162-71. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB The **chemokine receptor CCR5** contains seven transmembrane-spanning domains. It binds chemokines and acts as co-receptor for macrophage (m)-tropic (or R5) strains of **HIV**-1. Monoclonal antibodies (mAb) to **CCR5**, 3A9 and 5C7, were used for biopanning a nonapeptide cysteine (C)-constrained phage-displayed random **peptide** library to ascertain contact residues and define tertiary structures of possible **epitopes** on **CCR5**. Reactivity of antibodies with phagotopes was established by enzyme-linked immunosorbent assay (ELISA). mAb 3A9 identified a phagotope C-HASIYDFGS-C (3A9 / 1), and 5C7 most frequently identified C-PHWLRDLRV-C (5C7 / 1). Corresponding **peptides** were synthesized. Phagotopes and synthetic **peptides** reacted in ELISA with corresponding antibodies and synthetic **peptides inhibited** antibody binding to the phagotopes. Reactivity by immunofluorescence of 3A9 with **CCR5** was strongly **inhibited** by the corresponding **peptide**. Both mAb 3A9 and 5C7 reacted similarly with phagotopes and the corresponding **peptide** selected by the alternative mAb. The sequences of **peptide** inserts of phagotopes could be aligned as mimotopes of the sequence of **CCR5**. For phage 3A9 / 1, the motif SIYD aligned to residues at the N terminus and FG to residues on the first extracellular loop; for 5C7 / 1, residues at the N terminus, first extracellular loop, and possibly the third extracellular loop could be aligned and so would contribute to the mimotope. The synthetic **peptides** corresponding to the isolated phagotopes showed a CD4-dependent reactivity with **gp120** of a primary, m-tropic **HIV**-1 isolate. Thus reactivity of antibodies raised to **CCR5** against phage-displayed **peptides** defined mimotopes that reflect binding sites for these antibodies and reveal a part of the **gp120** binding sites on **CCR5**.

L16 ANSWER 74 OF 104 MEDLINE on STN
2000192716. PubMed ID: 10728472. The emerging role of fusion **inhibitors** in **HIV** infection. De Clercq E. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium.. erik.declercq@rega.kuleuven.ac.be) . Drugs in R&D, (1999 Nov) 2 (5) 321-31. Ref: 47. Journal code: 100883647. ISSN: 1174-5886. Pub. country: New Zealand. Language: English.
AB Fusion of **HIV** with its host cell requires the interaction of the viral **envelope** glycoprotein 120 (**gp120**) with the **chemokine receptor** CXCR4 [T cell-tropic (T-tropic) or X4 **HIV** strains] or **CCR5** [macrophage-tropic (M-tropic) or R5 **HIV** strains] followed by a 'spring-loaded' action of the glycoprotein 41 (gp41) that ensures fusion of the viral and cellular lipid membranes and permits the viral nucleocapsid to enter the cell. The overall fusion process can be blocked by a number of compounds. These include siamycin analogues, SPC 3 (a synthetic **peptide** derived from the V3 domain of **gp120**), pentafuside (T 20, DP 178) [a synthetic **peptide** corresponding to amino acid residues 127 to 162 of gp41], the betulinic acid derivative RPR 103611, TAK 779 (a low molecular weight non-**peptide CCR5** antagonist) and a number of compounds (T 22, T 134, ALX40-4C, CGP64222 and AMD 3100) that are targeted at the CXCR4 receptor. In particular, the bicyclam AMD 3100 has proved highly potent and selective as a CXCR4 antagonist that blocks the infectivity of X4 **HIV** strains in the nanomolar concentration range. The proof-of-concept that fusion **inhibitors** should be able to suppress viral replication in vivo has been demonstrated with pentafuside. Pentafuside and AMD 3100 have now proceeded to phase II clinical trials.

L16 ANSWER 75 OF 104 MEDLINE on STN

2000169708. PubMed ID: 10705550. Synthesis of **peptides** mimicking **chemokine receptor CCR5** and their **inhibitory** effects against **HIV**-1 infection. Konishi K; Ikeda K; Achiwa K; Hoshino H; Tanaka K. (School of Pharmaceutical Sciences, University of Shizuoka, Japan.) Chemical & pharmaceutical bulletin, (2000 Feb) 48 (2) 308-9. Journal code: 0377775. ISSN: 0009-2363. Pub. country: Japan. Language: English.

AB **Peptides** mimicking **chemokine receptor CCR5** were synthesized and their anti-**HIV**-1 activities evaluated. Prepared compounds, especially a sulfated derivatives, showed significant anti-**HIV**-1 activities. Furthermore, a hybrid molecule linked to an N-carbomethoxycarbonyl-prolyl-phenylalanine (CPF) moiety had a greater effect.

L16 ANSWER 76 OF 104 MEDLINE on STN

2000079398. PubMed ID: 10611407. A new insight into the role of "old" chemotactic **peptide** receptors FPR and FPRL1: down-regulation of **chemokine receptors CCR5** and CXCR4. Le Y; Shen W; Li B; Gong W; Dunlop N M; Wang J M. (Laboratory of Molecular Immunoregulation, Division of Basic Sciences, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, Maryland 21702-1201, USA.) Forum (Genoa, Italy), (1999 Oct-Dec) 9 (4) 299-314. Ref: 78. Journal code: 9315183. ISSN: 1121-8142. Pub. country: Italy. Language: English.

AB N-formyl **peptides**, such as fMet-Leu-Phe (fMLP), are some of the first identified and most potent chemoattractants for phagocytic leukocytes. In addition to the bacterial **peptide** fMLP and the putative endogenously produced formylated **peptides**, we recently identified a number of other novel **peptide** agonists that selectively activate the prototype formyl **peptide** receptor (FPR) and/or its variant FPRL1. These agonists include several synthetic **peptide** domains derived from the **envelope** proteins of the **human immunodeficiency virus** type 1 (**HIV**-1) and intact human acute phase serum protein serum amyloid A. The activation of FPR and/or FPRL1 in monocytes by these agonists resulted in increased cell migration, calcium mobilisation and the heterologous down-regulation of the expression and function of **chemokine receptors**, notably **CCR5** and CXCR4, two crucial fusion co-receptors for **HIV**-1. This down-regulation of **CCR5** by FPR and FPRL1 agonists was associated with a rapid serine phosphorylation of **CCR5**. The desensitisation of **CCR5** by FPR or FPRL1 agonists, not only **inhibited** its biological function induced by chemokine ligands, but also interfered with its capacity to act as a fusion co-receptor for monocyte tropic **HIV**-1. Thus, heterologous desensitisation by FPR and FPRL1 may play an important role in orchestrating the host innate immune responses which generate multiple chemotactic stimulants. Furthermore, the understanding of the structural and biochemical basis of FPR/FPRL1 activation may lead to the development of novel immunoregulatory and anti-**HIV** agents that emulate the process of heterologous desensitisation.

L16 ANSWER 77 OF 104 MEDLINE on STN

2000057926. PubMed ID: 10590121. Sequential CD4-coreceptor interactions in **human immunodeficiency virus** type 1 **Env** function: soluble CD4 activates **Env** for coreceptor-dependent fusion and reveals blocking activities of antibodies against cryptic conserved **epitopes** on **gp120**. Salzwedel K; Smith E D; Dey B; Berger E A. (Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.) Journal of virology, (2000 Jan) 74 (1) 326-33. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We devised an experimental system to examine sequential events by which the **human immunodeficiency virus** type 1 (**HIV**-1) **envelope** glycoprotein (**Env**) interacts with CD4 and coreceptor to induce membrane fusion. Recombinant soluble CD4 (sCD4) activated fusion between effector cells expressing **Env** and target cells expressing coreceptor (**CCR5** or CXCR4) but lacking CD4. sCD4-activated fusion was dose dependent, occurred comparably with two- and four-domain proteins, and demonstrated **Env**-coreceptor specificities parallel to those reported in conventional fusion and infectivity systems. Fusion activation occurred upon sCD4 preincubation and washing of the **Env**-expressing effector cells but not

the coreceptor bearing target cells, thereby demonstrating that sCD4 exerts its effects by acting on **Env**. These findings provide direct functional evidence for a sequential two-step model of **Env**-receptor interactions, whereby **gp120** binds first to CD4 and becomes activated for subsequent functional interaction with coreceptor, leading to membrane fusion. We used the sCD4-activated system to explore neutralization by the anti-**gp120** human monoclonal antibodies 17b and 48d. These antibodies reportedly bind conserved CD4-induced **epitopes** involved in coreceptor interactions but neutralize **HIV**-1 infection only weakly. We found that 17b and 48d had minimal effects in the standard cell fusion system using target cells expressing both CD4 and coreceptor but potently blocked sCD4-activated fusion with target cells expressing coreceptor alone. Both antibodies strongly **inhibited** sCD4-activated fusion by **Envs** from genetically diverse **HIV**-1 isolates. Thus, the sCD4-activated system reveals conserved **Env**-blocking **epitopes** that are masked in native **Env** and hence not readily detected by conventional systems.

L16 ANSWER 78 OF 104 MEDLINE on STN

2000032078. PubMed ID: 10562499. Nonproductive **human immunodeficiency virus** type 1 infection of human fetal astrocytes: independence from CD4 and major **chemokine receptors**. Sabri F; Tresoldi E; Di Stefano M; Polo S; Monaco M C; Verani A; Fiore J R; Lusso P; Major E; Chiodi F; Scarlatti G. (Microbiology and Tumorbiology Center, Karolinska Institute, Doktorsringen 13, Stockholm, 17177, Sweden.) Virology, (1999 Nov 25) 264 (2) 370-84. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** type 1 (**HIV**-1) infection of the brain is associated with neurological manifestations both in adults and in children. The primary target for **HIV**-1 infection in the brain is the microglia, but astrocytes can also be infected. We tested 26 primary **HIV**-1 isolates for their capacity to infect human fetal astrocytes in culture. Eight of these isolates, independent of their biological phenotype and **chemokine receptor** usage, were able to infect astrocytes. Although no sustained viral replication could be demonstrated, the virus was recovered by coculture with receptive cells such as macrophages or on stimulation with interleukin-1beta. To gain knowledge into the molecular events that regulate attachment and penetration of **HIV**-1 in astrocytes, we investigated the expression of several **chemokine receptors**. Fluorocytometry and calcium-mobilization assay did not provide evidence of expression of any of the major **HIV**-1 coreceptors, including CXCR4, **CCR5**, CCR3, and CCR2b, as well as the CD4 molecule on the cell surface of human fetal astrocytes. However, mRNA transcripts for CXCR4, **CCR5**, Bonzo/STRL33/TYMSTR, and APJ were detected by RT-PCR. Furthermore, infection of astrocytes by **HIV**-1 isolates with different **chemokine receptor** usage was not **inhibited** by the chemokines SDF-1beta, RANTES, MIP-1beta, or MCP-1 or by antibodies directed against the third variable region or the CD4 binding site of **gp120**. These data show that astrocytes can be infected by primary **HIV**-1 isolates via a mechanism independent of CD4 or major **chemokine receptors**. Furthermore, astrocytes are potential carriers of latent **HIV**-1 and on activation may be implicated in spreading the infection to other neighbouring cells, such as microglia or macrophages.

L16 ANSWER 79 OF 104 MEDLINE on STN

1999459181. PubMed ID: 10527688. **Peptide** T blocks **GP120/CCR5 chemokine receptor**-mediated chemotaxis. Redwine L S; Pert C B; Rone J D; Nixon R; Vance M; Sandler B; Lumpkin M D; Dieter D J; Ruff M R. (Department of Physiology and Biophysics, Georgetown University School of Medicine, Washington, DC, 20007, USA.) Clinical immunology (Orlando, Fla.), (1999 Nov) 93 (2) 124-31. Journal code: 100883537. ISSN: 1521-6616. Pub. country: United States. Language: English.

AB We previously reported that certain short **gp120** V2 region **peptides** homologous to vasaoactive intestinal **peptide** (VIP), such as "**peptide** T," were potent **inhibitors** of **gp120** binding, infectivity, and

neurotoxicity. The present study shows that synthetic V2 region derived **peptides** have potent intrinsic chemotaxis agonist activity for human monocytes and also act as antagonists of high-affinity (0.1 pM) **gp120**-mediated monocyte chemotaxis. Selectivity is shown in that **peptide** T is more potent at suppressing M-tropic than T-tropic **gp120** chemotaxis. **Peptide** T was also able to suppress monocyte chemotaxis to MIP-1beta, a chemokine with selectivity for **CCR5 chemokine receptors**, while chemotaxis of the more promiscuous ligand RANTES was not **inhibited**, nor was chemotaxis mediated by SDF-1alpha. In order to determine if **peptide** T mediated its **gp120** antagonistic effects via modulation of **CCR5** receptors, RANTES chemotaxis was studied using a **CCR5** receptor-transfected HOS cell line. In this case, RANTES chemotaxis was potently **inhibited** by V2-region-derived short **peptides**. **Peptide** T also partially suppressed (125)I-MIP1-beta binding to human monocytes, suggesting action at a subset of MIP1-beta receptors. The V2 region of **gp120** thus contains a potent receptor binding domain and synthetic **peptides** derived from this region modulate **CCR5 chemokine receptor** chemotactic signaling caused by either **gp120** or chemokine ligands. The results have therapeutic implications and may explain recent clinical improvements, in that **HIV/gp120** actions at **CCR5** receptors, such as occur in the brain or early infection, would be susceptible to **peptide** T **inhibition**.

L16 ANSWER 80 OF 104 MEDLINE on STN
1999376697. PubMed ID: 10446313. VIP and D-ala-**peptide** T-amide release chemokines which prevent **HIV**-1 **GP120**-induced neuronal death. Brenneman D E; Hauser J; Spong C Y; Phillips T M; Pert C B; Ruff M. (Section on Developmental and Molecular Pharmacology, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, USA.. dbrenn@codon.nih.gov) . Brain research, (1999 Aug 14) 838 (1-2) 27-36. Journal code: 0045503. ISSN: 0006-8993. Pub. country: Netherlands. Language: English.
AB Vasoactive intestinal **peptide** (VIP) and DAPTA (D-ala(1)-**peptide** T-amide, a **gp120**-derived octapeptide homologous to VIP) prevent neuronal cell death produced by five variants of **HIV**-1 (**human immunodeficiency virus**) **envelope** protein (**gp120**). VIP or DAPTA treatment of astrocyte cultures resulted in the release of macrophage inflammatory protein-1alpha (MIP-1alpha) and RANTES, beta chemokines known to block **gp120** interactions with microglial **chemokine receptors**. In rat cerebral cortical cultures, **gp120**-induced neuronal killing was partially or completely prevented by chemokines that stimulate the CXCR4, CCR3 or **CCR5 chemokine receptors**. Chemokines exhibited marked differences in potency and efficacy in preventing toxicity associated with five **gp120** variants (LAV/BRU, CM243, RF, SF2, and MN). RANTES had the broadest and most potent **inhibition** (IC(50)<3 pM for RF isolate). An octapeptide derived from RANTES also exhibited neuroprotection from **gp120** (RF isolate) toxicity (IC(50)=0.3 microM). Treatment with chemokines alone had no detectable effect on neuronal cell number. However, antiserum to MIP-1alpha produced neuronal cell death that was prevented by co-treatment with MIP-1alpha, suggesting that this endogenous chemokine exerts a tonic regulation important to neuronal survival. The neuroprotective action of VIP on **gp120** was attenuated by co-treatment with anti-MIP-1alpha. These studies suggest that the neuroprotective action of VIP is linked in part to its release of MIP-1alpha. Furthermore, neuroprotection produced by chemokines is dependent on both the type of chemokine and the variant structure of **gp120** and may be relevant to drug strategies for the treatment of AIDS dementia.

L16 ANSWER 81 OF 104 MEDLINE on STN
1999339712. PubMed ID: 10413367. Analysis of **HIV**-1 in the cervicovaginal secretions and blood of pregnant and nonpregnant women. Shaheen F; Sison A V; McIntosh L; Mukhtar M; Pomerantz R J. (The Dorrance H. Hamilton Laboratories, Center for Human Virology, Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

19107, USA.) Journal of human virology, (1999 May-Jun) 2 (3) 154-66. Journal code: 9805755. ISSN: 1090-9508. Pub. country: United States. Language: English.

AB OBJECTIVES: To detect **HIV**-1 in cellular and acellular fractions of cervicovaginal secretions obtained by cervicovaginal lavage (CVL) and evaluate viral genotypes in the **HIV**-1-positive CVL samples. STUDY DESIGN/METHODS: This study consists of 37 **HIV**-1-seropositive pregnant and nonpregnant women from the United States. A total of 63 paired CVL and blood samples were collected. **HIV**-1 DNA from cervical cells (CC) and virion RNA from cervical supernatant (CS) was detected by gag polymerase chain reaction (PCR) assays. The **HIV**-1 genotypes were determined by analyzing the nested PCR-amplified V3 region sequences of the **HIV**-1 **gp120 envelope** gene. RESULTS: Within this cohort, 95% of the women were on single or combination **antiretroviral** therapy. Of the pregnant women, 63% of samples had **HIV**-1 viral DNA in the CC, and 29% of samples were positive for viral RNA in the CS. Among nonpregnant women, 71% of samples were positive for **HIV**-1 DNA in CC, and 46% of samples tested positive for virion RNA in CS. Plasma viral load ranged between 10,000 and 100,000 copies/mL and showed significant correlation with the detection of **HIV**-1 RNA in the CVL; this relation was less apparent with viral DNA in CC. The viral blood and CVL specimens were further analyzed by evaluating the genotypes of **HIV**-1 variants. In most patients, a high degree of similarity was observed between the viral sequences derived from blood and CVL samples. Two patients demonstrated closely related but somewhat distinct genotypic variants in CVL and blood. One subject showed clear compartmentalization in which distinct viral genotypes were observed in CVL and blood. Based on V3 loop analyses of **gp120**, with one exception, the cervicovaginal secretions harbored viral populations with a macrophage (**CCR5**)-tropic phenotype. CONCLUSIONS: This study demonstrates the unique characteris tics of **HIV**-1 strains in the genital secretions of a relatively large cohort of **HIV**-1-infected women in the United States. These results are important for further analysis of **HIV**-1 transmission and pathogenesis in vivo and for rational vaccine design.

L16 ANSWER 82 OF 104 MEDLINE on STN

1999334824. PubMed ID: 10408339. V3 loop-derived **peptide** SPC3 **inhibits** infection of CD4- and galactosylceramide- cells by LAV-2/B. Moulard M; Mabrouk K; Martin I; Van Rietschoten J; Rochat H; Sabatier J M. (Centre d'Immunologie de Marseille Luminy, France.. mmoulard@scripps.edu) . journal of peptide research : official journal of the American Peptide Society, (1999 Jun) 53 (6) 647-55. Journal code: 9707067. ISSN: 1397-002X. Pub. country: Denmark. Language: English.

AB SPC3, a synthetic multibranched **peptide** including the GPGRAF consensus motif of the **human immunodeficiency virus** type 1 (**HIV**-1) **gp120** V3-loop is a potent **inhibitor** of **HIV** infection of human CD4+ lymphocytes, macrophages and CD4-/galactosylceramide+ human colon epithelial cells and is currently tested in phase II clinical trials (FDA protocol 257 A). The **antiviral** property of SPC3 was further investigated for its ability to **inhibit** LAV-2/B, an **HIV**-2 clone with a CD4-independent tropism. SPC3 **inhibited** the LAV-2/B-mediated infection of B-cell line which does not express the CD4 and the galactosylceramide molecules on their cell surface, suggesting an SPC3-sensitive CD4/galactosylceramide-independent pathway of viral infection in **HIV** susceptible cells. The molecular mechanism of the **peptide inhibition** was also investigated. The data suggested that the SPC3-mediated **inhibition** does not result from a direct competition between SPC3 and **gp120** binding to the cell surface of the target cell.

L16 ANSWER 83 OF 104 MEDLINE on STN

1999319001. PubMed ID: 10388657. Changes in and discrepancies between cell tropisms and coreceptor uses of **human immunodeficiency virus** type 1 induced by single point mutations at the V3 tip of the **env** protein. Shimizu N; Haraguchi Y; Takeuchi Y; Soda Y; Kanbe K; Hoshino H. (Department of Hygiene and Virology, Gunma University School of Medicine, Showa-machi, Maebashi, Gunma, 371-8511, Japan.) Virology, (1999 Jul 5)

259 (2) 324-33. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB We examined the effect of amino acid substitutions of the GPGR (glycine-proline-glycine-arginine) tip sequence at the V3 domain of the **Env** protein of **human immunodeficiency virus** type 1 (**HIV**-1) on its cell tropism and coreceptor use. We changed the GPGR sequence of a T-cell line (T)- and macrophage (M)-tropic (R5-R3-X4) **HIV**-1 strain, GUN-1wt, to GA(alanine)GR (the resulting mutant was designated GUN-1/A), GL(leucine)GR (GUN-1/L), GP(proline)GR (GUN-1/P), GR(arginine)GR (GUN-1/R), GS(serine)GR (GUN-1/S), or GT(threonine)GR (GUN-1/T). GUN-1/A, GUN-1/S, and GUN-1/T mutants infected brain-derived cells such as a CD4-transduced glioma cell line, U87/CD4, and a brain-derived primary cell strain, BT-20/N, as well as T-cell lines in a CD4-dependent manner, although the plating of these mutants onto macrophages was **inhibited**. GUN-1/L, GUN-1/P, and GUN-1/R mutants showed both T- and M-tropism, but did not plate onto the brain-derived cells. A CCR3, **CCR5**, CCR8, or CXCR4 gene was introduced into a CD4-positive glioma cell line, NP-2/CD4, which demonstrated complete resistance to various **HIV**-1 strains. Not only **HIV**-1 strains, which were infectious to macrophages, such as GUN-1wt, GUN-1v, GUN-1/L, and GUN-1/P, but also an **HIV**-1 strain, GUN-1v, which was hardly infectious to macrophages, grew well in NP-2/CD4 cells expressing CCR3 or **CCR5**. However, the M-tropic GUN-1/R mutant could not efficiently use **CCR5** nor CCR3. No point mutants, except GUN-1/L, grew well in NP-2/CD4 cells expressing CCR8. These findings indicate that the cell tropism of **HIV**-1 to macrophages and brain-derived cells and their use of the coreceptors were markedly, though not always concomitantly, affected by the tip sequence of the V3 domain.

L16 ANSWER 84 OF 104 MEDLINE on STN

1999292850. PubMed ID: 10364306. Shift of clinical **human immunodeficiency virus** type 1 isolates from X4 to R5 and prevention of emergence of the syncytium-inducing phenotype by blockade of CXCR4. Este J A; Cabrera C; Blanco J; Gutierrez A; Bridger G; Henson G; Clotet B; Schols D; De Clercq E. (Institut de Recerca de la SIDA-Caixa, Retrovirology Laboratory, Hospital Universitari Germans Trias i Pujol, 08916 Badalona, Spain.. jaeste@ns.hugtip.scs.es) . Journal of virology, (1999 Jul) 73 (7) 5577-85. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The emergence of X4 **human immunodeficiency virus** type 1 (**HIV**-1) strains in **HIV**-1-infected individuals has been associated with CD4(+) T-cell depletion, **HIV**-mediated CD8(+) cell apoptosis, and an impaired humoral response. The bicyclam AMD3100, a selective antagonist of CXCR4, selected for the outgrowth of R5 virus after cultivation of mixtures of the laboratory-adapted R5 (BaL) and X4 (NL4-3) **HIV** strains in the presence of the compound. The addition of AMD3100 to peripheral blood mononuclear cells infected with X4 or R5X4 clinical **HIV** isolates displaying the syncytium-inducing phenotype resulted in a complete suppression of X4 variants and a concomitant genotypic change in the V2 and V3 loops of the **envelope gp120** glycoprotein. The recovered viruses corresponded genotypically and phenotypically to R5 variants in that they could no longer use CXCR4 as coreceptor or induce syncytium formation in MT-2 cells. Furthermore, the phenotype and genotype of a cloned R5 **HIV**-1 virus converted to those of the R5X4 virus after prolonged culture in lymphoid cells. However, these changes did not occur when the infected cells were cultured in the presence of AMD3100, despite low levels of virus replication. Our findings indicate that selective blockade of the CXCR4 receptor prevents the switch from the less pathogenic R5 **HIV** to the more pathogenic X4 **HIV** strains, a process that heralds the onset of AIDS. In this article, we show that it could be possible to redirect the evolution of **HIV** so as to impede the emergence of X4 strains or to change the phenotype of already-existing X4 isolates to R5.

L16 ANSWER 85 OF 104 MEDLINE on STN

1999284361. PubMed ID: 10357469. Role of the **HIV** type 1 glycoprotein 120

V3 loop in determining coreceptor usage. Verrier F, Borman A M, Brand D, Girard M. (Unite de Virologie Moleculaire (CNRS URA 1966), Departement de Virologie, Institut Pasteur, Paris, France.) AIDS research and human retroviruses, (1999 May 20) 15 (8) 731-43. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Macrophage (M)-tropic **HIV**-1 isolates use the beta-**chemokine receptor CCR5** as a coreceptor for entry, while T cell line-adapted (TCLA) strains use CXCR4 and dual-tropic strains can use either **CCR5** or CXCR4. To investigate the viral determinants involved in choice of coreceptor, we used a fusion assay based on the infection of CD4+ HeLa cells that express one or both coreceptors with Semliki Forest virus (SFV) recombinants expressing the native **HIV**-1 **gp160** of a primary M-tropic isolate (**HIV**-1BX08), a TCLA isolate (**HIV**-1LAI), or a dual-tropic strain (**HIV**-1MN). We examined whether the V3 region of these glycoproteins interacts directly with the corresponding coreceptors by assaying coreceptor-dependent cell-to-cell fusion mediated by the different recombinants in the presence of various synthetic linear **peptides**. Synthetic **peptides** corresponding to different V3 loop sequences blocked syncytium formation in a coreceptor-specific manner. Synthetic V2 **peptides** were also **inhibitory** for syncytium formation, but showed no apparent coreceptor specificity. A BX08 V3 **peptide** with a D320 --> R substitution retained no **inhibitory** capacity for BX08 **Env**-mediated cell-to-cell fusion, but **inhibited** LAI **Env**-mediated fusion as efficiently as the homologous LAI V3 **peptide**. The same mutation engineered in the BX08 **env** gene rendered it able to form syncytia on CD4+CXCR4+**CCR5**-HeLa cells and susceptible to **inhibition** by SDF-1alpha and MIP-1beta. Other substitutions tested (D320 --> Q/D324 --> N or S306 --> R) exhibited intermediate effects on coreceptor usage. These results underscore the importance of the V3 loop in modulating coreceptor choice and show that single amino acid modifications in V3 can dramatically modify coreceptor usage. Moreover, they provide evidence that linear V3 loop **peptides** can compete with intact cell surface-expressed **gp120**/gp41 for **CCR5** or CXCR4 interaction.

L16 ANSWER 86 OF 104 MEDLINE on STN

1999272698. PubMed ID: 10339592. Stable exposure of the coreceptor-binding site in a CD4-independent **HIV**-1 **envelope** protein. Hoffman T L; LaBranche C C; Zhang W; Canziani G; Robinson J; Chaiken I; Hoxie J A; Doms R W. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA.) Proceedings of the National Academy of Sciences of the United States of America, (1999 May 25) 96 (11) 6359-64. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB We recently derived a CD4-independent virus from **HIV**-1/IIIB, termed IIIBx, which interacts directly with the **chemokine receptor** CXCR4 to infect cells. To address the underlying mechanism, a cloned **Env** from the IIIBx swarm (8x) was used to produce soluble **gp120**. 8x **gp120** bound directly to cells expressing only CXCR4, whereas binding of IIIB **gp120** required soluble CD4. Using an optical biosensor, we found that CD4-induced (CD4i) **epitopes** recognized by mAbs 17b and 48d were more exposed on 8x than on IIIB **gp120**. The ability of 8x **gp120** to bind directly to CXCR4 and to react with mAbs 17b and 48d in the absence of CD4 indicated that this **gp120** exists in a partially triggered but stable state in which the conserved coreceptor-binding site in **gp120**, which overlaps with the 17b **epitope**, is exposed. Substitution of the 8x V3 loop with that from the R5 virus strain BaL resulted in an **Env** (8x-V3BaL) that mediated CD4-independent **CCR5**-dependent virus infection and a **gp120** that bound to **CCR5** in the absence of CD4. Thus, in a partially triggered **Env** protein, the V3 loop can change the specificity of coreceptor use but does not alter CD4 independence, indicating that these properties are dissociable. Finally, IIIBx was more sensitive to neutralization by **HIV**-positive human sera, a variety of anti-IIIB **gp120** rabbit sera, and CD4i mAbs than was IIIB. The sensitivity of this virus to neutralization and the stable exposure of a highly conserved region of **gp120** suggest new strategies for the development of antibodies and small molecule **inhibitors** to this functionally important domain.

L16 ANSWER 87 OF 104 MEDLINE on STN
1999218467. PubMed ID: 10201969. Protective role of beta-chemokines associated with **HIV**-specific Th responses against perinatal **HIV** transmission. Wasik T J; Bratosiewicz J; Wierzbicki A; Whiteman V E; Rutstein R R; Starr S E; Douglas S D; Kaufman D; Sison A V; Polansky M; Lischner H W; Kozbor D. (Center for Neurovirology, Department of Neurology, MCP Hahnemann University, Philadelphia, PA 19102, USA.) Journal of immunology (Baltimore, Md. : 1950), (1999 Apr 1) 162 (7) 4355-64. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB To examine the protective role of cellular immunity in the vertical transmission of **HIV**, we analyzed **HIV**-specific IL-2 and CTL responses, as well as beta-chemokine expression in **HIV**-infected and uninfected infants of **HIV**+ mothers. Our results showed that **HIV envelope** (**env**) **peptide**-specific IL-2 responses associated with beta-chemokine production were detectable at birth in the majority of uninfected infants of **HIV**+ mothers. The responses falling to background before the infants were 1 yr old were rarely associated with **HIV**-specific CTL activity. Conversely, **HIV**-specific Th and CTL cellular responses were absent at birth in **HIV**-infected infants. Infants with AIDS-related symptoms exhibited undetectable or very low levels of **HIV**-specific cellular immunity during the first year of life, whereas those with a slowly progressive disease showed evidence of such immunity between their second and ninth month. The latter group of infected infants tested negative for plasma **HIV** RNA levels shortly after birth, suggesting lack of intrauterine exposure to **HIV**. The presence of **HIV**-specific Th responses at birth in uninfected newborns of **HIV**+ mothers, but absence of such activities in **HIV**-infected infants without evidence of intrauterine **HIV** infection, suggests that in utero development of **HIV**-specific Th responses associated with beta-chemokines could mediate nonlytic **inhibition** of infection during vertical transmission of **HIV**.

L16 ANSWER 88 OF 104 MEDLINE on STN
1999214354. PubMed ID: 10196311. Differential **inhibition** of **human immunodeficiency virus** type 1 fusion, **gp120** binding, and CC-chemokine activity by monoclonal antibodies to **CCR5**. Olson W C; Rabut G E; Nagashima K A; Tran D N; Anselma D J; Monard S P; Segal J P; Thompson D A; Kajumo F; Guo Y; Moore J P; Maddon P J; Dragic T. (Progenics Pharmaceuticals, Inc., Tarrytown, New York 10591, USA.) Journal of virology, (1999 May) 73 (5) 4145-55. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The CC-**chemokine receptor CCR5** mediates fusion and entry of the most commonly transmitted **human immunodeficiency virus** type 1 (**HIV**-1) strains. We have isolated six new anti-**CCR5** murine monoclonal antibodies (MAbs), designated PA8, PA9, PA10, PA11, PA12, and PA14. A panel of **CCR5** alanine point mutants was used to map the **epitopes** of these MAbs and the previously described MAb 2D7 to specific amino acid residues in the N terminus and/or second extracellular loop regions of **CCR5**. This structural information was correlated with the MAbs' abilities to **inhibit** (i) **HIV**-1 entry, (ii) **HIV**-1 **envelope** glycoprotein-mediated membrane fusion, (iii) **gp120** binding to **CCR5**, and (iv) CC-chemokine activity. Surprisingly, there was no correlation between the ability of a MAb to **inhibit HIV**-1 fusion-entry and its ability to **inhibit** either the binding of a **gp120**-soluble CD4 complex to **CCR5** or CC-chemokine activity. MAbs PA9 to PA12, whose **epitopes** include residues in the **CCR5** N terminus, strongly **inhibited gp120** binding but only moderately **inhibited HIV**-1 fusion and entry and had no effect on RANTES-induced calcium mobilization. MAbs PA14 and 2D7, the most potent **inhibitors** of **HIV**-1 entry and fusion, were less effective at **inhibiting gp120** binding and were variably potent at **inhibiting** RANTES-induced signaling. With respect to **inhibiting HIV**-1 entry and fusion, PA12 but not PA14 was potently synergistic when used in combination with 2D7, RANTES, and CD4-immunoglobulin G2, which **inhibits HIV**-1 attachment. The data support a model wherein **HIV**-1 entry occurs in three stages: receptor (CD4) binding, coreceptor (**CCR5**) binding, and

coreceptor mediated membrane fusion. The antibodies described will be useful for further dissecting these events.

L16 ANSWER 89 OF 104 MEDLINE on STN
1999210126. PubMed ID: 10195751. Marked increase in anti-**HIV** activity, as well as **inhibitory** activity against **HIV** entry mediated by CXCR4, linked to enhancement of the binding ability of tachyplesin analogs to CXCR4. Xu Y; Tamamura H; Arakaki R; Nakashima H; Zhang X; Fujii N; Uchiyama T; Hattori T. (Laboratory of Virus Immunology, Research Center for Acquired Immunodeficiency Syndrome, Institute for Virus Research, Kyoto University, Japan.) AIDS research and human retroviruses, (1999 Mar 20) 15 (5) 419-27. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB T22 ([Tyr5,12, Lys7]-polyphemusin II) is a strong anti-**HIV** compound. Six analogs of T22 and two natural forms were synthesized. Of them, all downsized **peptides** (14 residues; TW70, T131, T134, and T140) showed a higher selectivity index than did other, 17- or 18-residue **peptides**. In particular, T134 and T140 showed both lower cytotoxicity and higher **antiviral** activity than did T22 against **HIV** infection of MT-4 cells, an HTLV-I-bearing T cell line. To clarify the **inhibitory** mode of T22 and its analogs, we used a single-round replication assay (luciferase assay), in which different **envelope**-bearing pseudotypes were used to infect CXCR4- or **CCR5**-bearing U87 cells via CD4. All of the analogs **inhibited** T cell line-tropic strain HXB-2 (X4) and dual-tropic strain 89.6 (R5X4) **HIV** infections mediated by CXCR4, but had no effect on macrophage-tropic strain ADA (R5) or 89.6 **HIV** infections mediated by **CCR5**. The **inhibition** by T134 (IC50 of 2.70 nM) and T140 (IC50 of 0.432 nM) was also stronger than that by T22 (IC50 of 5.05 nM). The binding of anti-CXCR4 monoclonal antibody 12G5 to lymphoma-derived T cell line Sup-T1 was more efficiently blocked by T134 and T140 than by T22. Taken together, T22 and its analogs T134 and T140 exerted their **inhibition** by specific binding to CXCR4. The marked increase in the anti-**HIV** activity of T134 and T140 was ascribed to an enhancement in their ability to bind to CXCR4.

L16 ANSWER 90 OF 104 MEDLINE on STN
1999194814. PubMed ID: 10092648. **Epitope** mapping of **CCR5** reveals multiple conformational states and distinct but overlapping structures involved in chemokine and coreceptor function. Lee B; Sharron M; Blanpain C; Doranz B J; Vakili J; Setoh P; Berg E; Liu G; Guy H R; Durell S R; Parmentier M; Chang C N; Price K; Tsang M; Doms R W. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.) Journal of biological chemistry, (1999 Apr 2) 274 (14) 9617-26. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The **chemokine receptor CCR5** is the major coreceptor for R5 **human immunodeficiency virus** type-1 strains. We mapped the **epitope** specificities of 18 **CCR5** monoclonal antibodies (mAbs) to identify domains of **CCR5** required for chemokine binding, **gp120** binding, and for inducing conformational changes in **Env** that lead to membrane fusion. We identified mAbs that bound to N-terminal **epitopes**, extracellular loop 2 (ECL2) **epitopes**, and multidomain (MD) **epitopes** composed of more than one single extracellular domain. N-terminal mAbs recognized specific residues that span the first 13 amino acids of **CCR5**, while nearly all ECL2 mAbs recognized residues Tyr-184 to Phe-189. In addition, all MD **epitopes** involved ECL2, including at least residues Lys-171 and Glu-172. We found that ECL2-specific mAbs were more efficient than NH2- or MD-antibodies in blocking RANTES or MIP-1beta binding. By contrast, N-terminal mAbs blocked **gp120-CCR5** binding more effectively than ECL2 mAbs. Surprisingly, ECL2 mAbs were more potent **inhibitors** of viral infection than N-terminal mAbs. Thus, the ability to block virus infection did not correlate with the ability to block **gp120** binding. Together, these results imply that chemokines and **Env** bind to distinct but overlapping sites in **CCR5**, and suggest that the N-terminal domain of **CCR5** is more important for **gp120** binding while the extracellular loops are more important for inducing conformational changes in **Env** that lead

to membrane fusion and virus infection. Measurements of individual antibody affinities coupled with kinetic analysis of equilibrium binding states also suggested that there are multiple conformational states of **CCR5**. A previously described mAb, 2D7, was unique in its ability to effectively block both chemokine and **Env** binding as well as coreceptor activity. 2D7 bound to a unique antigenic determinant in the first half of ECL2 and recognized a far greater proportion of cell surface **CCR5** molecules than the other mAbs examined. Thus, the **epitope** recognized by 2D7 may represent a particularly attractive target for **CCR5** antagonists.

L16 ANSWER 91 OF 104 MEDLINE on STN

1999164117. PubMed ID: 10064617. A functional, discontinuous **HIV**-1 **gp120** C3/C4 domain-derived, branched, synthetic **peptide** that binds to CD4 and **inhibits** MIP-1alpha chemokine binding. Howie S E; Fernandes M L; Heslop I; Hewson T J; Cotton G J; Moore M J; Innes D; Ramage R; Harrison D J. (Department of Pathology, Centre for Protein Technology, University of Edinburgh, UK.. s.e.m.howie@ed.ac.uk) . FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (1999 Mar) 13 (3) 503-11. Journal code: 8804484. ISSN: 0892-6638. Pub. country: United States. Language: English.

AB This paper describes a branched synthetic **peptide** [3.7] that incorporates sequence discontinuous residues of **HIV**-1 **gp120** constant regions. The approach was to bring together residues of **gp120** known to interact with human cell membranes such that the **peptide** could fold to mimic the native molecule. The **peptide** incorporates elements of both the conserved CD4 and **CCR5** binding sites. The 3.7 **peptide**, which cannot be produced by conventional genetic engineering methods, is recognized by antiserum raised to native **gp120**. The **peptide** also binds to CD4 and competitively **inhibits** binding of QS4120 an antibody directed against the CDR2 region of CD4. When preincubated with the CD4+ve MM6 macrophage cell line, which expresses mRNA for the CCR3 and **CCR5 chemokine receptors**, both 3.7 and **gp120 inhibit** binding of the chemokine MIP-1alpha. The **peptide** also **inhibits** infection of primary macrophages by M-tropic **HIV**-1. Thus, 3.7 is a prototype candidate **peptide** for a vaccine against **HIV**-1 and represents a novel approach to the rational design of **peptides** that can mimic complex sequence discontinuous ligand binding sites of clinically relevant proteins.

L16 ANSWER 92 OF 104 MEDLINE on STN

1999151705. PubMed ID: 10029247. Increased association of glycoprotein 120-CD4 with **HIV** type 1 coreceptors in the presence of complex-enhanced anti-CD4 monoclonal antibodies. Golding H; Ouyang J; Zaitseva M; Broder C C; Dimitrov D S; Lapham C. (Division of viral products, CBER, Food and Drug Administration, Bethesda, Maryland 20892, USA.. goldingh@cber.fda.gov) . AIDS research and human retroviruses, (1999 Jan 20) 15 (2) 149-59. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB CD4-specific monoclonal antibodies (CG1, CG7, and CG8), which bind with a 5- to 10-fold higher avidity to preformed CD4-**gp120** complexes than to CD4, were previously shown to recognize newly identified conformational **epitopes** in the D1-CDR3 region of CD4. In the current study, these and other complex-enhanced MAbs were tested in three separate assays of **HIV**-1 coreceptor (CXCR4/**CCR5**) recruitment. In these assays, the CD4-specific MAbs CG1, -7, and -8 stabilized the association of coreceptor, **gp120**, and CD4 in trimolecular complexes. In contrast, the **gp120**-specific, complex-enhanced MAbs 48d and 17b were **inhibitory**. These data suggest that conformational changes in the CDR3 region of CD4-D1, induced by **gp120** binding, may be involved in coreceptor association and thus play a positive role in the **HIV**-1 cell fusion process.

L16 ANSWER 93 OF 104 MEDLINE on STN

1999099077. PubMed ID: 9882391. Comparison of the antibody repertoire generated in healthy volunteers following immunization with a monomeric recombinant **gp120** construct derived from a **CCR5**/CXCR4-using **human**

immunodeficiency virus type 1 isolate with sera from naturally infected individuals. Beddows S; Lister S; Cheingsong R; Bruck C; Weber J. (Department of GU Medicine and Communicable Diseases, Imperial College School of Medicine at St. Mary's, London W2 1PG, United Kingdom.) Journal of virology, (1999 Feb) 73 (2) 1740-5. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We have characterized sera from healthy volunteers immunized with a monomeric recombinant **gp120** (rgp120) derived from a **CCR5**/CXCR4 (R5X4)-using subtype B isolate of **human immunodeficiency virus** type (**HIV**-1), **HIV**-1W61D, in comparison to sera from long-term **HIV**-1-infected individuals, using homologous reagents. Sera from vaccinees and **HIV**-1 positive subjects had similar binding titers to native monomeric rgp120W61D and showed a similar titer of antibodies **inhibiting** the binding of soluble CD4 (sCD4) to rgp120W61D. However, extensive **peptide** binding studies showed that the overall pattern of recognition of vaccinee and **HIV**-1-positive sera is different, with vaccinee sera displaying a wider and more potent recognition of linear V1/V2 and V3 domain **epitopes**. Neutralization of homologous **HIV**-1W61D or heterologous **HIV**-1M2424/4 peripheral blood mononuclear cell (PBMC)-derived virus lines by vaccinee sera could be achieved, but only after adaptation of the viruses to T-cell lines and was quickly lost on readaptation to growth in PBMC. Sera from **HIV**-positive individuals were able to neutralize both PBMC-grown and T-cell line-adapted viruses. Interestingly, rgp120W61D was recognized by monoclonal antibodies previously shown to neutralize primary **HIV**-1 isolates. The use of very potent adjuvants and R5X4 rgp120 led to an antibody response equivalent in binding activity and **inhibition** of binding of sCD4 to **gp120** to that of **HIV**-positive individuals but did not lead to the induction of antibodies capable of neutralizing PBMC-grown virus.

L16 ANSWER 94 OF 104 MEDLINE on STN

1999085860. PubMed ID: 9870313. Interaction of **human immunodeficiency virus** type 1 **envelope** glycoprotein V3 loop with **CCR5** and CD4 at the membrane of human primary macrophages. Rabehi L; Seddiki N; Benjouad A; Gluckman J C; Gattegno L. (Laboratoire de Biologie Cellulaire, Faculte de Medecine, Universite Paris-Nord, Bobigny, France.) AIDS research and human retroviruses, (1998 Dec 20) 14 (18) 1605-15. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB We show that infection of primary monocyte-derived macrophages (MDMs) and blood lymphocytes (PBLs) by **human immunodeficiency virus** type 1 (**HIV**-1) R5 strains, but not that of PBLs by X4 strain **HIV**-1LAI, is **inhibited** by beta-chemokines RANTES and MIP-1alpha. A biotinylated disulfide-bridged **peptide** mimicking the complete loop of clade B consensus V3 domain of **gp120** (V3Cs), but not a biotinylated V3LAI **peptide** or a control beta-endorphin **peptide** of approximately the same molecular weight (MW), was found to bind specifically to MDM membrane proteins, in particular two proteins of 42 and 62 kDa migrating as sharp bands after electroblotting onto Immobilon, and this was specifically **inhibited** by anti-V3 antibodies. When biotinylated V3Cs was incubated with intact MDMs, which were then washed and lysed, and the resulting material was incubated with streptavidin-agarose beads and electroblotted onto Immobilon, fresh V3Cs also bound to proteins of the same molecular weight recovered in the V3Cs-interacting material. This binding was **inhibited** by anti-V3 antibodies, and no binding occurred with the control **peptides**. V3Cs also bound to soluble recombinant CD4, and CD4 monoclonal antibody Q4120 specifically recognized the V3Cs-interacting 62-kDa protein, which should thus correspond to CD4. Recombinant radiolabeled RANTES, MIP-1alpha, and MIP-1beta, but not IL-8, also bound to a 42-kDa protein on the membrane of MDMs as well as to the V3Cs-interacting 42-kDa protein, and excess unlabeled V3Cs **inhibited** such binding. This protein was also recognized by antibodies to **CCR5**, the RANTES/MIP-1alpha/MIP-1beta receptor. These data show that V3Cs binds to MDM membrane proteins that comprise CD4 and **CCR5**, and that multimolecular complexes involving at least **gp120** V3, CD4, and **CCR5** are formed on the surface of MDMs as part of V3-mediated postbinding events occurring during **HIV**-1 infection.

L16 ANSWER 95 OF 104 MEDLINE on STN

1998389858. PubMed ID: 9721247. Interactions among **HIV gp120**, CD4, and CXCR4: dependence on CD4 expression level, **gp120** viral origin, conservation of the **gp120** COOH- and NH2-termini and V1/V2 and V3 loops, and sensitivity to neutralizing antibodies. Mondor I; Moulard M; Ugolini S; Klasse P J; Hoxie J; Amara A; Delaunay T; Wyatt R; Sodroski J; Sattentau Q J. (Case 906, The Centre d'Immunologie de Marseille-Luminy, Marseille Cedex 9, 13288, France.) Virology, (1998 Sep 1) 248 (2) 394-405. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB The binding of **HIV**-derived recombinant soluble (s)**gp120** to the CD4(+)/CXCR4(+) A3.01 T cell line **inhibits** the binding of the CXCR4-specific monoclonal antibodies 12G5, which interacts with the second extracellular loop, and 6H8, which binds the NH2 terminus. We have used this as an assay to analyse the interaction of recombinant sgp120 from diverse viral origins with CXCR4. The strength of the interaction between sgp120 and CXCR4 correlated with sgp120 affinity for the CD4-CXCR4 complex, and the interaction of sgp120MN and sgp120IIIB with CXCR4 was highly dependent on the level of CD4 expressed on a variety of different T cell lines. sgp120 from X4, R5X4, and R5 viruses interacted with CXCR4, although the R5 sgp120-CXCR4 interactions were weaker than those of the other gp120s. The interaction of sgp120IIIB or sgp120MN with CXCR4 was **inhibited** by neutralizing monoclonal antibodies that prevent the sgp120-CD4 interaction but also by antibodies specific for the **gp120** V2 and V3 loops, the CD4-induced **epitope** and the 2G12 **epitope**, which interfere weakly or not at all with CD4-sgp120 binding. The binding to A3.01 cells of wild-type sgp120HxB2, but not of sgp120 deleted in the COOH and NH2 termini, interfered with 12G5 binding in a dose-dependent manner. Further deletion of the V1 and V2 loops restored CXCR4 binding activity, but additional removal of the V3 loop eliminated the **gp120**-CXCR4 interaction, without decreasing the affinity between mutated sgp120 and CD4. Taken together, these results demonstrate that the interactions between sgp120 and CXCR4 are globally similar to those previously observed between sgp120 and **CCR5**, with some apparent differences in the strength of the sgp120-CXCR4 interactions and their dependence on CD4.

L16 ANSWER 96 OF 104 MEDLINE on STN

1998376489. PubMed ID: 9710449. **HIV**-1 **envelope** gp41 is a potent **inhibitor** of chemoattractant receptor expression and function in monocytes. Ueda H; Howard O M; Grimm M C; Su S B; Gong W; Evans G; Ruscetti F W; Oppenheim J J; Wang J M. (The Laboratory of Molecular Immunoregulation, Division of Basic Sciences, National Cancer Institute, Frederick Cancer Research, Frederick, Maryland 21702-1201, USA.) Journal of clinical investigation, (1998 Aug 15) 102 (4) 804-12. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB **HIV**-1 uses CD4 and **chemokine receptors** as cofactors for cellular entry. The viral **envelope** transmembrane protein gp41 is thought to participate in viral fusion with CD4(+) cells. We investigated whether gp41 interacts with **chemokine receptors** on human monocytes by testing its effect on the capacity of cells to respond to chemokine stimulation. Monocytes preincubated with gp41 of the MN strain showed markedly reduced binding, calcium mobilization, and chemotaxis in response to a variety of chemokines as well as to the bacterial **peptide** fMLP. This generalized **inhibition** of monocyte activation by chemoattractants required the presence of CD4, since the effect of gp41 was only observed in CD4(+) monocytes and in HEK293 cells cotransfected with **chemokine receptors** and an intact CD4, but not a CD4 lacking its cytoplasmic domain. Confocal microscopy showed that gp41 caused internalization of CXCR4 in HEK293 cells provided they were also cotransfected with intact CD4. In addition, pretreatment of monocytes with protein kinase C **inhibitors** partially reversed the **inhibitory** effect of gp41. Thus, gp41, which had not previously been implicated as interacting with **HIV**-1 fusion cofactors, downregulates chemoattractant receptors on monocytes by a CD4-dependent pathway.

L16 ANSWER 97 OF 104 MEDLINE on STN
1998325144. PubMed ID: 9658072. Determinants of **human immunodeficiency virus** type 1 **envelope** glycoprotein activation by soluble CD4 and monoclonal antibodies. Sullivan N; Sun Y; Binley J; Lee J; Barbas C F 3rd; Parren P W; Burton D R; Sodroski J. (Division of Human Retrovirology, Dana-Farber Cancer Institute, Department of Pathology, Harvard Medical School, Boston, Massachusetts 02115, USA.) Journal of virology, (1998 Aug) 72 (8) 6332-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Infection by some **human immunodeficiency virus** type 1 (**HIV**-1) isolates is enhanced by the binding of subneutralizing concentrations of soluble receptor, soluble CD4 (sCD4), or monoclonal antibodies directed against the viral **envelope** glycoproteins. In this work, we studied the abilities of different antibodies to mediate activation of the **envelope** glycoproteins of a primary **HIV**-1 isolate, YU2, and identified the regions of **gp120 envelope** glycoprotein contributing to activation. Binding of antibodies to a variety of **epitopes** on **gp120**, including the CD4 binding site, the third variable (V3) loop, and CD4-induced **epitopes**, enhanced the entry of viruses containing YU2 **envelope** glycoproteins. Fab fragments of antibodies directed against either the CD4 binding site or V3 loop also activated YU2 virus infection. The activation phenotype was conferred on the **envelope** glycoproteins of a laboratory-adapted **HIV**-1 isolate (HXBc2) by replacing the **gp120** V3 loop or V1/V2 and V3 loops with those of the YU2 virus. Infection by the YU2 virus in the presence of activating antibodies remained **inhibitable** by macrophage **inhibitory** protein 1beta, indicating dependence on the **CCR5** coreceptor on the target cells. Thus, antibody enhancement of YU2 entry involves neither Fc receptor binding nor **envelope** glycoprotein cross-linking, is determined by the same variable loops that dictate enhancement by sCD4, and probably proceeds by a process fundamentally similar to the receptor-activated virus entry pathway.

L16 ANSWER 98 OF 104 MEDLINE on STN
1998206736. PubMed ID: 9546659. The V3 loop of **human immunodeficiency virus** type-1 **envelope** protein is a high-affinity ligand for immunophilins present in human blood. Endrich M M; Gehring H. (Biochemisches Institut, Universitat Zurich, Switzerland.) European journal of biochemistry / FEBS, (1998 Mar 15) 252 (3) 441-6. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB **Human immunodeficiency virus** type-1 (**HIV**-1) infection requires binding of the **envelope** protein **gp120** to host CD4 receptors and the action of the **chemokine receptors** CXCR4 or **CCR5**, which define cell tropism. The proline-containing V3 loop of **gp120** determines the selection of the **chemokine receptor** and participates in conformational changes on binding of **gp120** to CD4. In this study, we show that macrophage-tropic and T-cell-tropic V3 loop **peptides** bind specifically to the active site of the immunophilins FK506-binding protein (FKBP12), and cyclophilins A and B. Macrophage-tropic and T-cell-tropic V3 loop **peptides inhibited** the peptidyl-prolyl cis-trans isomerase (PPIase) activities of the immunophilins. Kd values in the range 0.036-4.1 microM were determined with V3 loop **peptides** labeled with an **environmentally** sensitive fluorophore. The observed binding properties of the V3 loop **peptides** reveal structural motifs of linear water-soluble peptidic substrates for tight interaction with immunophilins. FKBP12, and cyclophilins A and B were found to be present in normal human blood in the ranges 0.8-1.7, 1.4-2.3 and 2.4-3.1 nM, respectively, as demonstrated by PPIase activity measurements and western blot analysis. Cyclophilins A and B levels in serum of **HIV**-1-infected individuals were increased 3.6-fold and 1.6-fold. Due to the interaction of immunophilins with V3 loop **peptides** and with the **envelope** protein **gp120**, a role of immunophilins in **HIV** pathogenesis as conformases or docking mediators seems possible, since immunophilin receptors on cell membranes and immunophilin-related virulence factors of pathogens have been identified.

L16 ANSWER 99 OF 104 MEDLINE on STN
1998189358. PubMed ID: 9512422. Antigen-specific release of beta-chemokines by anti-**HIV**-1 cytotoxic T lymphocytes. Price D A; Sewell A K; Dong T; Tan R; Goulder P J; Rowland-Jones S L; Phillips R E. (Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK.) Current biology : CB, (1998 Mar 12) 8 (6) 355-8. Journal code: 9107782. ISSN: 0960-9822. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A major advance in understanding **human immunodeficiency virus** (**HIV**) biology was the discovery that the beta-chemokines MIP-1 alpha (macrophage inflammatory protein-1 alpha), MIP-1 beta (macrophage inflammatory protein-1 beta) and RANTES (regulated on activation, normal T-cell expressed and secreted) **inhibit** entry of **HIV**-1 into CD4+ cells by blocking the critical interaction between the **CCR5** coreceptor and the V3 domain of the viral **envelope** glycoprotein **gp120** [1,2]. CD8+ lymphocytes are a major source of beta-chemokines [3], but the stimulus for chemokine release has not been well defined. Here, we have shown that engagement of CD8+ cytotoxic T lymphocytes (CTLs) with **HIV**-1-encoded human leukocyte antigen (HLA) class I-restricted **peptide** antigens caused rapid and specific release of these beta-chemokines. This release paralleled cytolytic activity and could be attenuated by naturally occurring amino acid variation within the HLA class I-restricted **peptide** sequence. **Epitope** variants that bound to appropriate HLA class I molecules but failed to stimulate cytolytic activity in CTLs also failed to stimulate chemokine release. We conclude that signalling through the T-cell receptor (TCR) following binding of antigen results in beta-chemokine release from CTLs in addition to cytolytic activity, and that both responses can be abolished by **epitope** mutation. These results suggest that antigenic variation within **HIV**-1 might not only allow the host cell to escape lysis, but might also contribute to the propagation of infection by failing to activate beta-chemokine-mediated **inhibition** of **HIV**-1 entry.

L16 ANSWER 100 OF 104 MEDLINE on STN
97404634. PubMed ID: 9261346. **Envelope** glycoproteins from **human immunodeficiency virus** types 1 and 2 and simian immunodeficiency virus can use human **CCR5** as a coreceptor for viral entry and make direct CD4-dependent interactions with this **chemokine receptor**. Hill C M; Deng H; Unutmaz D; Kewalramani V N; Bastiani L; Gorny M K; Zolla-Pazner S; Littman D R. (Skirball Institute of BioMolecular Medicine, New York, New York 10016, USA.) Journal of virology, (1997 Sep) 71 (9) 6296-304. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Several members of the **chemokine receptor** family have recently been identified as coreceptors, with CD4, for entry of **human immunodeficiency virus** type 1 (**HIV**-1) into target cells. In this report, we show that the **envelope** glycoproteins of several strains of **HIV**-2 and simian immunodeficiency virus (SIV) employ the same **chemokine receptors** for infection. **Envelope** glycoproteins from **HIV**-2 use **CCR5** or CXCR4, while those from several strains of SIV use **CCR5**. Our data indicate also that some viral **envelopes** can use more than one coreceptor for entry and suggest that some of these coreceptors remain to be identified. To further understand how different **envelope** molecules use **CCR5** as an entry cofactor, we show that soluble purified **envelope** glycoproteins (SU component) from **CCR5**-tropic **HIV**-1, **HIV**-2, and SIV can compete for binding of iodinated chemokine to **CCR5**. The competition is dependent on binding of the SU glycoprotein to cell surface CD4 and implies a direct interaction between **envelope** glycoproteins and **CCR5**. This interaction is specific since it is not observed with SU glycoprotein from a CXCR4-tropic virus or with a **chemokine receptor** that is not competent for viral entry (CCR1). For **HIV**-1, the interaction can be **inhibited** by antibodies specific for the V3 loop of SU. Soluble CD4 was found to potentiate binding of the **HIV**-2 ST and SIVmac239 **envelope** glycoproteins to **CCR5**, suggesting that a CD4-induced conformational change in SU is required for subsequent binding to **CCR5**. These data suggest a common fundamental mechanism by which structurally diverse **HIV**-1, **HIV**-2, and SIV **envelope** glycoproteins

interact with CD4 and CCR5 to mediate viral entry.

L16 ANSWER 101 OF 104 MEDLINE on STN
97404394. PubMed ID: 9256481. Antibodies to several conformation-dependent **epitopes** of **gp120**/gp41 **inhibit** CCR-5-dependent cell-to-cell fusion mediated by the native **envelope** glycoprotein of a primary macrophage-tropic **HIV**-1 isolate. Verrier F C; Charneau P; Altmeyer R; Laurent S; Borman A M; Girard M. (Departement de Virologie Moleculaire, Institut Pasteur, Paris, France.) Proceedings of the National Academy of Sciences of the United States of America, (1997 Aug 19) 94 (17) 9326-31. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The beta-**chemokine receptor** CCR-5 is essential for the efficient entry of primary macrophage-tropic **HIV**-1 isolates into CD4(+) target cells. To study CCR-5-dependent cell-to-cell fusion, we have developed an assay system based on the infection of CD4(+) CCR-5(+) HeLa cells with a Semliki Forest virus recombinant expressing the **gp120**/gp41 **envelope** (**Env**) from a primary clade B **HIV**-1 isolate (BX08), or from a laboratory T cell line-adapted strain (LAI). In this system, **gp120**/gp41 of the "nonsyncytium-inducing," primary, macrophage-tropic **HIV**-1BX08 isolate, was at least as fusogenic as that of the "syncytium-inducing" **HIV**-1LAI strain. BX08 **Env**-mediated fusion was **inhibited** by the beta-chemokines RANTES (regulated upon activation, normal T cell expressed and secreted) and macrophage inflammatory proteins 1beta (MIP-1beta) and by antibodies to CD4, whereas LAI **Env**-mediated fusion was insensitive to these beta-chemokines. In contrast soluble CD4 significantly reduced LAI, but not BX08 **Env**-mediated fusion, suggesting that the primary isolate **Env** glycoprotein has a reduced affinity for CD4. The domains in **gp120**/gp41 involved in the interaction with the CD4 and CCR-5 molecules were probed using monoclonal antibodies. For the antibodies tested here, the greatest **inhibition** of fusion was observed with those directed to conformation-dependent, rather than linear **epitopes**. Efficient **inhibition** of fusion was not restricted to **epitopes** in any one domain of **gp120**/gp41. The assay was sufficiently sensitive to distinguish between antibody- and beta-chemokine-mediated fusion **inhibition** using serum samples from patient BX08, suggesting that the system may be useful for screening human sera for the presence of biologically significant antibodies.

L16 ANSWER 102 OF 104 MEDLINE on STN
97064177. PubMed ID: 8906796. CD4-dependent, antibody-sensitive interactions between **HIV**-1 and its co-receptor CCR-5. Trkola A; Dragic T; Arthos J; Binley J M; Olson W C; Allaway G P; Cheng-Mayer C; Robinson J; Maddon P J; Moore J P. (The Aaron Diamond AIDS Research Centre, The Rockefeller University, New York 10016, USA.) Nature, (1996 Nov 14) 384 (6605) 184-7. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The beta-**chemokine receptor** CCR-5 is an essential co-factor for fusion of **HIV**-1 strains of the non-syncytium-inducing (NSI) phenotype with CD4+ T-cells. The primary binding site for **human immunodeficiency virus** (**HIV**)-1 is the CD4 molecule, and the interaction is mediated by the viral surface glycoprotein **gp120** (refs 6, 7). The mechanism of CCR-5 function during **HIV**-1 entry has not been defined, but we have shown previously that its beta-chemokine ligands prevent **HIV**-1 from fusing with the cell. We therefore investigated whether CCR-5 acts as a second binding site for **HIV**-1 simultaneously with or subsequent to the interaction between **gp120** and CD4. We used a competition assay based on **gp120 inhibition** of the binding of the CCR-5 ligand, macrophage inflammatory protein (MIP)-1beta, to its receptor on activated CD4+ T cells or CCR-5-positive CD4- cells. We conclude that CD4 binding, although not absolutely necessary for the **gp120**-CCR-5 interaction, greatly increases its efficiency. Neutralizing monoclonal antibodies against several sites on **gp120**, including the V3 loop and CD4-induced **epitopes**, **inhibited** the interaction of **gp120** with CCR-5, without affecting **gp120**-CD4 binding. Interference with **HIV**-1 binding to one or both of its receptors (CD4 and CCR-5) may be an important mechanism of

virus neutralization.

L16 ANSWER 103 OF 104 MEDLINE on STN

97064176. PubMed ID: 8906795. CD4-induced interaction of primary **HIV**-1 **gp120** glycoproteins with the **chemokine receptor** CCR-5. Wu L; Gerard N P; Wyatt R; Choe H; Parolin C; Ruffing N; Borsetti A; Cardoso A A; Desjardin E; Newman W; Gerard C; Sodroski J. (LeukoSite, Inc., Cambridge, Massachusetts 02142, USA.) Nature, (1996 Nov 14) 384 (6605) 179-83. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB For efficient entry into target cells, primary macrophage-tropic and laboratory-adapted human immunodeficiency viruses type 1 (**HIV**-1) require particular **chemokine receptors**, CCR-5 and CXCR-4, respectively, as well as the primary receptor CD4 (refs 1-6). Here we show that a complex of **gp120**, the exterior **envelope** glycoprotein, of macrophage-tropic primary **HIV**-1 and soluble CD4 interacts specifically with CCR-5 and **inhibits** the binding of the natural CCR-5 ligands, macrophage inflammatory protein (MIP)-1alpha and MIP-1beta (refs 7, 8). The apparent affinity of the interaction between **gp120** and CCR-5 was dramatically lower in the absence of soluble CD4. Additionally, in the absence of **gp120**, an interaction between a two-domain CD4 fragment and CCR-5 was observed. A **gp120** fragment retaining the CD4-binding site and overlapping **epitopes** was able to interact with CCR-5 only if the V3 loop, which can specify **HIV**-1 tropism and **chemokine receptor** choice, was also present on the molecule. Neutralizing antibodies directed against either CD4-induced or V3 **epitopes** on **gp120** blocked the interaction of gp120-CD4 complexes with CCR-5. These results suggest that **HIV**-1 attachment to CD4 creates a high-affinity binding site for CCR-5, leading to membrane fusion and virus entry.

L16 ANSWER 104 OF 104 MEDLINE on STN

97054456. PubMed ID: 8898753. The V3 domain of the **HIV**-1 **gp120** **envelope** glycoprotein is critical for chemokine-mediated blockade of infection. Cocchi F; DeVico A L; Garzino-Demo A; Cara A; Gallo R C; Lusso P. (Institute of Human Virology, University of Maryland Biotechnology Institute & School of Medicine, Baltimore, Maryland 21201, USA.) Nature medicine, (1996 Nov) 2 (11) 1244-7. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB The ability of CD8 T cells derived from **human immunodeficiency virus** (**HIV**)-infected patients to produce soluble **HIV**-suppressive factor(s) (**HIV**-SF) has been suggested as an important mechanism of control of **HIV** infection in vivo. The C-C chemokines RANTES, MIP-1 alpha and MIP-1 beta were recently identified as the major components of the **HIV**-SF produced by both immortalized and primary patient CD8 T cells. Whereas they potently **inhibit** infection by primary and macrophage-tropic **HIV**-1 isolates, T-cell line-adapted viral strains tend to be insensitive to their suppressive effects. Consistent with this discrepancy, two distinct **chemokine receptors**, namely, CXCR4 (ref. 7) and **CCR5** (ref. 8), were recently identified as potential co-receptors for T-cell line-adapted and macrophage-tropic **HIV**-1 isolates, respectively. Here, we demonstrate that the third hypervariable domain of the gp 120 **envelope** glycoprotein is a critical determinant of the susceptibility of **HIV**-1 to chemokines. Moreover, we show that RANTES, MIP-1 alpha and MIP-1 beta block the entry of **HIV**-1 into cells and that their **antiviral** activity is independent of pertussis toxin-sensitive signal transduction pathways mediated by **chemokine receptors**. The ability of the chemokines to block the early steps of **HIV** infection could be exploited to develop novel therapeutic approaches for AIDS.

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